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Renal Artery Stenosis Management Strategies: An Updated Comparative Effectiveness Review

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

This report may periodically be assessed for the urgency to update. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program website at: www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Abstract

Background: Treatment options for atherosclerotic renal artery stenosis (ARAS) include medical therapy alone or renal artery revascularization with continued medical therapy, most commonly by percutaneous transluminal renal angioplasty with stent placement (PTRAS). This review updates a prior Comparative Effectiveness Review of management strategies for ARAS from 2006 and 2007.
Objectives: Compare the effectiveness and safety of PTRAS versus medical therapy, and also surgical revascularization, to treat ARAS, and predictors of outcomes by intervention.
Data sources: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews from inception to 29 December 2014; eligible studies from the original reports; screened studies from relevant existing systematic reviews; and other sources.
Review methods: We included all studies comparing ARAS interventions, single-group prospective PTRAS and medical therapy studies, and prospective or retrospective surgery studies. We also included 20 recent case reports of patients with acute ARAS decompensation. Outcomes included all-cause and cardiovascular mortality, cardiovascular events, renal replacement therapy (RRT), other kidney events and function, hypertension events, blood pressure (BP), medication use, and adverse events.
Results: From 1454 citations, we included 76 studies and 20 case reports. Seven randomized controlled trials (RCTs) and 11 other comparative studies compared treatment options; 67 individual cohorts of patients (in 63 studies) treated with PTRAS; 20 cohorts of patients (in 17 studies) treated with medical therapy alone, and four cohorts of patients treated surgically.
Comparative studies: RCTs of PTRAS versus medical therapy were applicable only to patients with clinical equipoise between the treatments; 5 trials found no difference in mortality, RRT, cardiovascular events, or pulmonary edema; mostly found no difference in kidney function; but possible better BP control after PTRAS; procedural adverse events were rare but medication-related adverse events were not reported. Nonrandomized studies did not adjust for baseline differences between groups; they found no significant difference in mortality, but improved kidney function and BP control after PTRAS.
Noncomparative studies: Estimates of outcome event rates are summarized. All 20 case reports describe patients who had clinical and symptomologic improvement after revascularization.
Subgroup analyses: 2 RCTs found no patient characteristics associated with outcomes between PTRAS and medical therapy. In one retrospective comparative study, patients with flash pulmonary edema or both rapidly declining kidney function and refractory hypertension had decreased mortality with PTRAS (vs. medical therapy). Single-intervention studies found that various factors predicted outcomes.
Conclusions: For all outcomes, the strength of evidence is low regarding the relative benefit of PTRAS and medical therapy alone for patients with ARAS. The RCTs had limited applicability to typical patients for whom PTRAS is recommended. All nonrandomized trials were inadequately adjusted to account for underlying differences between patients undergoing different interventions. There is a low strength of evidence that there is no difference in clinically important outcomes (death, cardiovascular events, RRT), between PTRAS and medical therapy alone, but this conclusion is most applicable to those patients for whom there is clinical equipoise between the two treatments. There is low strength of evidence that kidney function and BP control may be improved in patients who undergo PTRAS. There is low strength of evidence that clinically important adverse events are more common, though rare, related to PTRAS than medical therapy alone. New studies or reanalyses of existing evidence are needed to better understand the comparative effectiveness of PTRAS versus medical therapy. There is evidence that subsets of patients benefit from revascularization, but the evidence does not clearly define who these patients are, except that case reports demonstrate that some patients with acute decompensation clearly benefit from revascularization, but a study of an unbiased sample of these patients is needed.

Executive Summary

Background: Atherosclerotic renal artery stenosis (ARAS) is increasingly common in an aging population with rising prevalence of diabetes, hypertension, obesity, dyslipidemia, and vascular disease. The goals of treatment are improvement in uncontrolled hypertension, preservation or salvage of kidney function, and improvement in symptoms. Treatment alternatives include medical therapy alone or renal artery revascularization with continued medical therapy. Medical therapy generally involves aggressive therapy with multiple antihypertensives, antilipidemics, and antiplatelet agents. Most commonly revascularization is achieved through percutaneous transluminal renal angioplasty with stent placement (PTRAS) across the stenosis. Open surgical revascularization, once common, is generally reserved for patients with complicated renal artery anatomy or who require aortic repair. After revascularization, patients generally continue aggressive medical therapy. The Tufts Evidence-based Practice Center conducted a Comparative Effectiveness Review of management strategies for ARAS in 2006 with an update in 2007. The review concluded that the evidence did not support one treatment approach over another for the general population of people with ARAS. There was weak or inadequate evidence for most interventions and outcomes and whether any clinical or intervention characteristics affect outcomes.

Objectives: We sought to summarize the evidence evaluating the comparative effect and safety of PTRAS, surgical revascularization, and medical therapy to treat ARAS, in regards to clinically important outcomes. We evaluated what clinical, imaging, laboratory and anatomic characteristics, and what PTRAS treatment variables are associated with outcomes.

Data sources: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews from inception to 29 December 2014. We also included still-eligible studies from the original reports and screened studies from relevant existing systematic reviews, recent kidney, urology, and vascular surgery conference proceedings, and FDA, WHO, and ClinicalTrials.gov databases. Furthermore, we solicited studies via Scientific Information Packets from manufacturers.

Review methods: We included comparative studies of any design of PTRAS, medical therapy, and/or surgical revascularization (where renal artery revascularization was the most common primary indication for surgery). We also included prospective studies of PTRAS (N≥30), medical therapy alone (N≥10), and surgery (N≥10 if prospective, N≥100 if retrospective). We further included the 20 most recently published case reports of patients with acute decompensation due to ARAS. The assessed outcomes included all-cause and cardiovascular mortality, cardiovascular events (including congestive heart failure [CHF] and coronary or cerebral artery revascularization), renal replacement therapy (RRT), and other kidney events, hypertensive crises and other hypertension-related events, kidney function, blood pressure (BP) control, medication use, and adverse events.

Results: From 1454 citations from the updated search, other literature sources, and the original reports, we included 76 relevant studies and 20 case reports. Seven randomized controlled trials (RCTs) and 11 other comparative studies compared treatment options; 67 individual cohorts of patients (in 63 studies) were treated with PTRAS in prospective studies; 20 cohorts of patients

(in 17 studies) were treated with medical therapy alone in prospective studies, and four eligible cohorts of patients were treated surgically.

Comparative studies: RCTs of PTRAS versus medical therapy were limited in their applicability only to patients for whom there was clinical equipoise between the two options.Five trials found no difference in mortality, RRT, cardiovascular events, or pulmonary edema, and mostly found no difference in change in kidney function, but mixed results regarding BP control with some evidence of better BP control after PTRAS; procedural adverse events were rare and no medication-related adverse events were reported. Effect size estimates were generally imprecise and there was inconsistency in effect size estimates across studies. One RCT that compared open surgical revascularization with medical therapy alone, found no significant differences in mortality, RRT, or BP control. One RCT that compared PTRAS and surgery found no significant difference in mortality, kidney function, or BP. Nonrandomized comparative studies failed to adequately account for fundamental differences between patients who undergo PTRAS and those who remain on medical therapy alone or between those who undergo PTRAS or surgery; thus, limiting their ability to support the findings from RCTs. Nonrandomized studies of PTRAS versus medical therapy found no significant difference in mortality, but improved kidney function and BP control after PTRAS. Studies of PTRAS versus surgery found no difference in mortality or BP control, but one study found that kidney function improvement was more common after surgery than PTRAS.

Noncomparative studies: The review summarizes clinical event rates and changes in kidney function and BP for the single-intervention studies. All 20 case reports describe patients who had clinical and symptomologic improvement (particularly related to pulmonary edema, severe acute kidney injury or RRT, and malignant hypertension) after revascularization.

Subgroup analyses: Two RCTs found no patient characteristics that were significantly associated with different outcomes between PTRAS and medical therapy. A retrospective comparative study found that patients presenting with flash pulmonary edema or with both rapidly declining kidney function and refractory hypertension had decreased mortality with PTRAS (versus medical therapy) than other patients. In single-intervention studies, worse pre-PTRAS kidney function or BP were generally associated with better improvement in these outcomes and that worse kidney function was associated with increased death. Studies were inconsistent regarding whether bilateral disease was associated with outcomes. In general, patients with histories of cardiovascular disease were at increased risk of clinical outcomes including death. In two medical therapy studies, patients with flash pulmonary edema, but not rapid kidney function decline or refractory hypertension, was associated with increased death or, separately, cardiovascular events but not RRT (one study) and patients with worse kidney function or with proteinuria were at significantly increased risk of RRT, but not death. Two studies examined the association between specific medications and clinical outcomes, both of which found a strong association between statin use and reduced death, RRT, and cardiovascular outcomes, but conflicting findings regarding association of angiotensin inhibitors and outcomes; one study found no association between beta blocker use and outcomes. In three PTRAS studies, use of gold-coated stents, sirolimus eluting stents, embolic protection devices, and intraluminal brachytherapy were not associated with improved outcomes.

Conclusions: Because of important limitations to the evidence base, for all outcomes, there is low strength of evidence regarding the relative benefit of PTRAS and medical therapy alone for patients with ARAS. Important issues lowering the strength of evidence included that the RCTs had limited applicability only to patients for whom revascularization is not considered necessary in current clinical practice (since the patients and their clinicians had to agree to the possibility of not having PTRAS). More typical patients for whom PTRAS is recommended were excluded from the trials either by design or because of difficulty recruiting them into trials since, in clinical practice, there is often a strong belief that PTRAS is superior to continued medical therapy alone. Further lowering the strength of evidence, effect size estimates across studies were generally imprecise and findings were commonly inconsistent across studies. Also, all nonrandomized trials were inadequately adjusted to account for underlying differences between patients undergoing different interventions, limiting their value to potentially support the findings of the RCTs. Thus, there is a low strength of evidence that there is no difference in clinically important outcomes (death, cardiovascular events, RRT), between PTRAS and medical therapy alone, but this conclusion is most applicable to those patients for whom there is clinical equipoise between the two treatments. There is low strength of evidence that kidney function and BP control may be improved in patients who undergo PTRAS versus medical therapy based on comparative studies and the indirect comparison between cohorts of patients who had PTRAS or continued medical therapy. There is low strength of evidence that clinically important adverse events are more common, though rare, related to PTRAS than medical therapy alone; however, studies generally failed to report medication-related adverse events.

New studies or reanalyses of existing evidence are needed to better understand the comparative effectiveness of PTRAS versus medical therapy for those patients who most commonly undergo PTRAS, namely those who have a “clinical indication” for revascularization under current standard practice. There is evidence that subsets of patients clearly benefit from revascularization (at least in terms of improved kidney function and BP control), but the evidence does not clearly define who these patients are. As evidenced from case reports, patients with acute decompensation clearly benefit from revascularization, but a study that includes an unbiased sample of these patients is needed.

Contents

Tables

Figures

Appendixes

Introduction

Background

Renal artery stenosis (RAS) is defined as the narrowing of the lumen of the renal artery. Atherosclerosis accounts for 90 percent of cases of RAS and usually involves the ostium and proximal third of the main renal artery and the perirenal aorta.[1] ARAS is a progressive disease that may occur alone or in combination with hypertension (HTN) and ischemic kidney disease. Atherosclerotic RAS (ARAS) is becoming increasingly common because of atherosclerosis in an aging population with increasing prevalence of diabetes, obesity, hyperlipidemia, aortoiliac occlusive disease, coronary artery disease, and HTN. Based on a recent systematic review,[2] the prevalence of RAS among the general hypertensive population is unknown, but among people with clinical characteristics of renovascular HTN—including severe HTN, therapy-resistant HTN, HTN-onset at a young age, recent onset of HTN, or presence of an abdominal bruit—RAS prevalence is 14.1 percent (95% confidence interval [CI] 12.7-15.8%). Among people with diabetes mellitus (DM) and HTN, the prevalence is 20.0 percent (95% CI 15.4-25.5%) and among people undergoing coronary angiography, the prevalence is 10.5 percent (95% CI 9.8-11.2%). In the United States, 12 to 14 percent of new patients entering dialysis programs have been found to have ARAS.[4]

Optimal strategies for evaluating patients suspected of having RAS remain unclear. Patients with moderate to high risk atherovascular diseases who present with uncontrolled HTN or unexplained abnormal kidney function tests are generally evaluated for RAS.[1, 3, 4] A reduction in estimated glomerular filtration rate (GFR) of at least 30 percent from baseline following the introduction of angiotensin converting enzyme inhibitor (ACEi) or angiotensin-receptor blocker (ARB) therapy is a clinical clue suggestive of RAS.[5] However, it is important to note that the primary reason for diagnosing ARAS is to set the patient up for revascularization, since medical management of ARAS is identical to medical management of other patients with difficult to control HTN who are at increased risk of cardiovascular events and kidney damage. A variety of physiological studies to assess the renin-angiotensin system and perfusion studies to assess renal blood flow are available. However, the clinical clues can be nonspecific and physiologic studies have limited usefulness in ARAS, especially among the elderly. Initial evaluation often relies on imaging techniques such as duplex ultrasonography, magnetic resonance angiography, computed tomographic angiography, and radionuclide renal scanning. The value of these noninvasive imaging techniques depend on operator's experience, body habitus, the presence of bowel gas, and they may be less reliable in visualizing distal segments of renal arteries. Currently, catheter angiography remains the reference standard for evaluating the degree of stenosis in RAS.

The goals of therapy are improvement in uncontrolled HTN, preservation or salvage of kidney function, and improvement in symptoms and quality of life. Treatment alternatives include medical therapy alone or renal artery revascularization with continued medical therapy. Combination therapy with multiple antihypertensive agents, typically including ACEi or ARBs, calcium channel blockers, and/or beta blockers, are frequently prescribed with a goal of normalizing blood pressure (BP). Statins are commonly prescribed to lower low density lipoprotein (LDL) cholesterol, and antiplatelet agents, such as aspirin or clopidogrel, are prescribed to reduce thrombosis. Among patients treated with medical therapy alone, there is a risk for deterioration of kidney function since the treatments do not reduce the stenosis and thus cannot substantially improve blood flow to the kidneys. ACEi and ARBs are effective in controlling renovascular HTN in 86 to 92 percent of these patients, but the loss of kidney

function due to reduction in transcapillary filtration pressure can result in acute or chronic kidney disease.[1]

Renal artery revascularization may provide immediate improvement in kidney function and BP; however, as with all invasive interventions, it may also result in procedural complications of bleeding, dissection, or embolization in some patients. The current standard for revascularization in most patients is percutaneous transluminal renal angioplasty with stent placement (PTRAS) across the stenosis. Angioplasty without stent placement is rarely employed due to the high rate of restenosis. Placement of renal artery stents can also resolve dissections, minimize stenosis recoil and restenosis, and correct translesional pressure gradients. Most patients undergoing renal artery revascularization have been exposed to many years of relative kidney ischemia and poorly controlled HTN. Thus, revascularization may not have substantial long-term clinical benefit due to prior kidney and cardiovascular damage and ongoing atherosclerotic processes.

Revascularization by surgical reconstruction is generally reserved for patients with complicated renal artery anatomy or who require pararenal aortic reconstructions for aortic aneurysms or severe aortoiliac occlusive disease. The percentage of patients undergoing surgical revascularization has dropped precipitously over time. In the U.S. Medicare population, among people having renal revascularization, 33 percent had surgical revascularization in 1992; by 2004, this had dropped to 1.5 percent.[6]

Even after revascularization, patients generally continue triple therapy with antihypertensive agents, antiplatelet agents, and statins, though fewer (or lower dose) antihypertensive agents may be necessary to control BP. Furthermore, patients may be better able to tolerate ACEi or ARBs after revascularization. Particularly for patients with diabetes or with CHF, the ability to use ACEi or ARBs can be renoprotective and reduce cardiovascular disease.

Indications for and timing of revascularization for ARAS are topics of considerable debate. The American Heart Association lists three clinical criteria for revascularization: 1) HTN (accelerated, refractory, or malignant), 2) preservation of kidney function, and 3) cardiac syndromes (recurrent "flash" pulmonary edema or unstable angina with significant RAS).[7] This must be weighed against the morbidity and mortality risks of revascularization.

The Tufts Evidence-based Practice Center (EPC) conducted a Comparative Effectiveness Review of management strategies for RAS in 2006 (with an update in 2007).[8, 9] The review evaluated medical therapies (without revascularization), angioplasty (with or without stent, but focusing primarily on with stent), surgical revascularization, and natural history studies. The review included 68 studies, but none of the studies evaluated the principal question of interest—namely, the relative effects of intensive medical therapy and PTRAS. The review concluded that the evidence did not support one treatment approach over another for the general population of people with ARAS. There was weak or inadequate evidence for most interventions and outcomes and whether any clinical or intervention characteristics affect outcomes.

Since the original EPC review, the two major then-ongoing trials of PTRAS versus medical therapy alone, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) and the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trials, have been published. These trials have influenced clinical decisionmaking regarding management of ARAS. Without clear benefit on BP or kidney function in these trials, indications for interventional treatment have been interpreted to be limited. The trials also failed to identify specific subpopulations that may benefit from revascularization. As a result, since their

publication, fewer patients are referred for procedures, and medical therapy alone, using antihypertensive agents, antiplatelet agents, and statins, has become the standard of care. Importantly though, the trials had difficulties recruiting patients, mostly because clinicians and patients often had strong preferences for or against undergoing revascularization that precluded their enrollment for randomized treatment. Therefore, questions remain about the applicability of these trials and the true value of PTRAS for patients who have (or whose clinicians have) a strong preference for PTRAS.

A subset of patients effectively excluded from the trials includes patients with acute decompensation related to ARAS. These patients have rapidly declining kidney function with possible oliguria or anuria, flash pulmonary edema, and/or intractable malignant HTN. It is generally understood that these patients usually benefit from rapid revascularization, which must be undertaken before the kidneys are permanently injured. However, less well understood is which patients may or may not benefit from revascularization.

Thus, controversy remains regarding optimal strategies for evaluation and management of patients with ARAS. In particular, a fuller understanding in needed of which patients are most likely to benefit from revascularization and for which continued aggressive medical therapy alone may be most appropriate.

Scope and Key Questions

This report summarizes the evidence evaluating the comparative effectiveness and safety of PTRAS, surgical revascularization, and medical therapy in the treatment of ARAS, particularly after long-term followup. Key questions addressed in this report remain unchanged from the original reviews and are as follows:

1. For patients with ARAS in the modern management era (i.e., since JNC-5 in 1993*), what is the evidence on the effects of aggressive medical therapy (i.e., antihypertensive, antiplatelet, and antilipid treatment) compared to PTRAS on long-term clinical outcomes (at least 6 months) including BP control, preservation of kidney function, flash pulmonary edema, other cardiovascular events, and survival?

   1a. What are the patient characteristics, including etiology, predominant clinical presentation, and severity of stenosis, in the studies?

   1b. What adverse events and complications have been associated with aggressive medical therapy or PTRAS?

2. What clinical, imaging, laboratory and anatomic characteristics are associated with improved or worse outcomes when treating with either aggressive medical therapy alone or PTRAS?

3. What treatment variables are associated with improved or worse outcomes of PTRAS, including periprocedural medications, type of stent, use of distal protection devices, or other adjunct techniques?

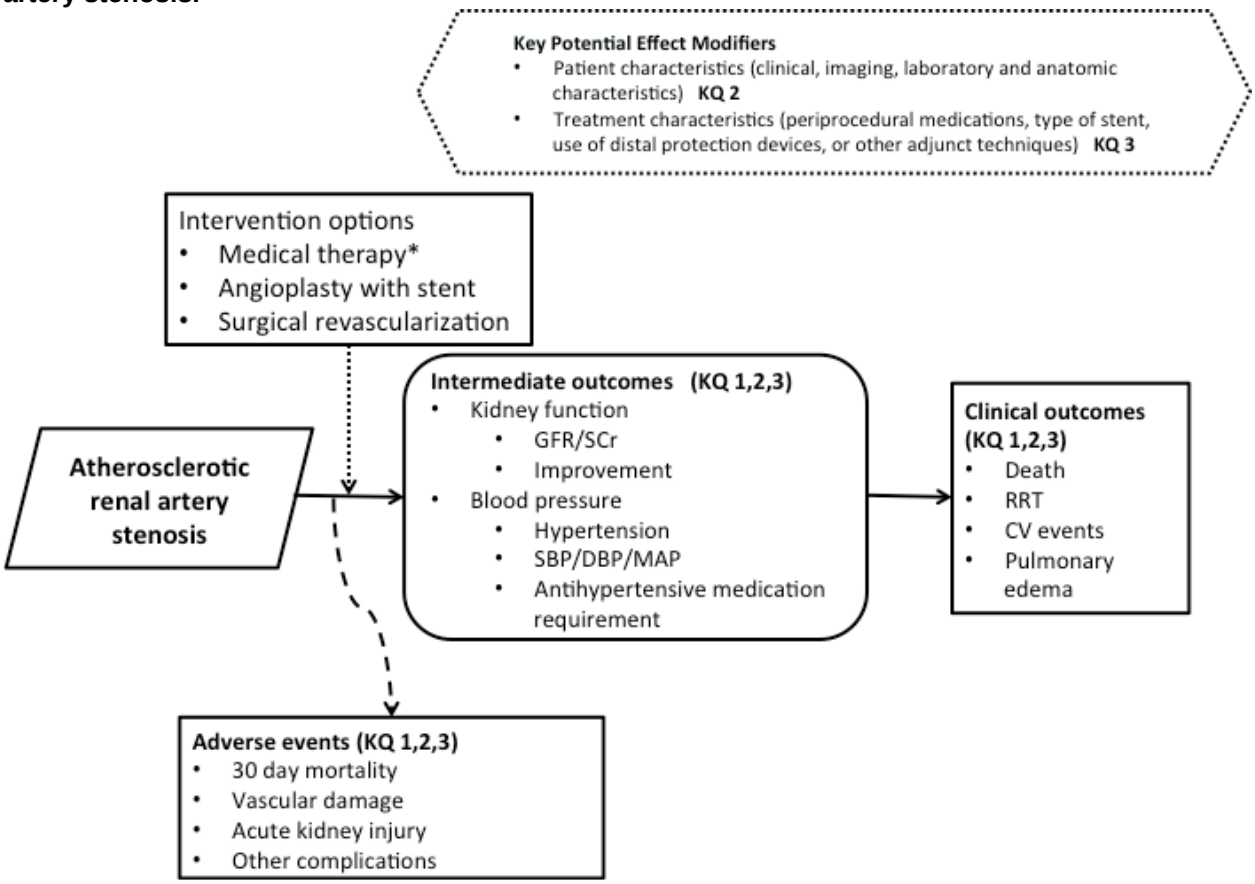
* 5th Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (1993). These guidelines marked a substantial change from previous guidelines in treatment

recommendations for HTN, including more aggressive BP targets. This time point also marks when ACE inhibitors began to be used more routinely for patients with severe HTN.

Analytic Framework

We applied the analytic framework depicted in **Figure 1** to answer the key questions in the evaluation of the treatment modalities for ARAS. This framework addressed relevant clinical outcomes. It also examined clinical predictors that affected treatment outcomes. While evidence from high quality randomized controlled trials (RCT) was preferred, these data were rare, so nonrandomized and uncontrolled studies were used to augment the evidence.

Figure 1. Analytic framework for evaluating the effectiveness and safety of treatments for renal artery stenosis.



GFR = glomerular filtration rate; KQ = key question; SBP/DBP/MAP = systolic, diastolic, and mean arterial pressures; SCr = serum creatinine.
* Usually a combination of antihypertensive medications, antilipid medications (statins), and antiplatelet medications.

Types of participants

The population of interest for this report is adults with ARAS that is of sufficient severity to warrant aggressive management, either due to resistant HTN, evidence of reduced kidney function, or the high likelihood of poor outcomes. Because of the variety of techniques used to diagnose and define RAS, the definitions used by study authors were accepted. Patients with ARAS commonly also have aortic disease, which must be treated simultaneously. The original

2006 report was restricted to studies that performed only renal artery procedures. However, it is increasingly common that subclinical aortic disease is treated at the same time as the renal artery lesion in a single invasive intervention. Therefore, this report aims to include studies of all ARAS treatments, regardless of whether an aortic procedure was also conducted, as long as the primary indication for the intervention was the ARAS. Studies of patients with severe aortic disease requiring surgery who also had a concomitant renal artery stent placed were excluded since the ARAS was not the primary indication for the intervention.

Types of interventions

The primary interventions of interest are aggressive medical therapy, PTRAS, and open vascular repairs. However, this review covers any medical (noninvasive) intervention, PTRAS, and any open vascular surgery whose primary indication is amelioration of RAS. This review does not update the literature on angioplasty without stent or natural history studies.

Types of outcome measures

The primary outcomes of interest include long-term (6 months or more) mortality, kidney function, HTN, cardiovascular disease, and related outcomes, in addition to adverse events and complications (including 30-day mortality).

Types of studies

The ideal study to answer the key questions would be a RCT directly comparing the primary interventions of interest. However, given the paucity of RCTs and of nonrandomized comparative studies (NRCS), this review evaluates studies of cohorts of patients who received one treatment (or one set of treatments) without a control group.

Case reports

Due to concerns that the trial and observational studies do not adequately address outcomes in patients with ARAS who have acute decompensation, this review also includes a summary of the more recent case reports of patients treated for acute decompensation, including malignant HTN or acutely uncontrollable HTN, flash pulmonary edema, acute kidney injury, and recent-onset end-stage renal disease requiring dialysis.

Methods

Technical Expert Panel

This report on the comparison of aggressive medical therapy, PTRAS, and surgical revascularization for the management of ARAS is based on a systematic review of the literature. We convened a Technical Expert Panel (TEP), which included nephrologists, invasive cardiologists and radiologists with expertise in RAS, vascular surgeons, the medical officer from the CORAL study (in the Division of Cardiovascular Sciences at NHLBI), and an FDA representative (in the Division of Cardiovascular Devices). The TEP includes experts nominated by the Society of Interventional radiology, the Kidney and Urology Foundation of America, the National Kidney Foundation, and the American College of Cardiology/American Heart Association. The TEP provided input to help refine the protocol, identify important issues, and define parameters for the review of evidence. The TEP was also asked to suggest additional studies for evaluation by the EPC.

Search strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the key questions that have been published since the original RAS reports, which had a final search date of April 23, 2007. We searched MEDLINE®, the Cochrane Central Trials Registry® and Cochrane Database of Systematic Reviews®, and EMBASE (2007 – 29 December 2014). The reference lists of prior systematic reviews were hand-searched, and the TEP was asked to identify additional studies. We also searched the "grey literature" for relevant completed studies in the FDA database (with assistance from our FDA TEP representative), clinicaltrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/default.aspx), and conference proceedings from 2012 through 2014 for the National Kidney Foundation, the American Society of Nephrology, the Kidney and Urology Foundation, the American Urological Association, and the Society of Vascular Surgery. In our searches, we combined terms for renal artery stenosis (RAS), renal HTN, and renal vascular disease, limited to adult humans and relevant research designs, including case reports and series (see Appendix A for the complete search strategy). Furthermore, we solicited studies via Scientific Information Packets from manufacturers (one study was sent to us, which was already known to us).

Study selection

We assessed titles and/or abstracts of citations identified from literature searches for inclusion, using the criteria described below. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria. Both abstract and full-text screening was conducted in duplicate with conflicts resolved by reconciliation with the whole research team. All rejected full-text articles were confirmed by the project lead.

Studies included in the original reports were reassessed for inclusion based on the current eligibility criteria. Those that remain eligible are fully included in the current update.

Population and condition of interest

We included studies of adults (≥ 18 years) with ARAS, as defined by the study authors, whether unilateral, bilateral, or in patients with a solitary functioning kidney. We excluded studies in which >20 percent of patients had fibromuscular dysplasia, arteritis-associated RAS, embolic or thrombotic stenosis, or other nonatherosclerotic stenosis. We excluded studies of patients with previous surgical or angioplasty interventions for RAS (i.e., with restenosis or in-stent stenosis) or with RAS in the setting of a transplanted kidney, renal artery aneurysms (requiring repair), or concurrent cancer (including renal cell carcinoma). We allowed studies that performed simultaneous repair of aortic disease (e.g., aneurysm) only if the RAS was the primary indication for surgery and the aortic disease surgery was incidental.

Interventions of interest

The primary interventions of interest were "aggressive medical therapy"—defined as antihypertensive drugs, antilipid (lipid lowering) drugs, and antiplatelet drugs—and PTRAS. However, the review covers a broader range of interventions that are currently used in practice, including a range of medical therapies alone, PTRAS, and open surgical revascularization.

Specifically, we included studies of any medical intervention or set of medical interventions in patients who did not have revascularization. In particular, use (and tolerance) of ACEi or ARB was of interest.

We included studies of PTRAS (where ≥80% of patients had stent placement). We excluded "drive-by" angioplasty—renal artery angioplasty done at the time of coronary angiography (or angioplasty) in patients who do not have previously known RAS. There was consensus among the TEP members that the currently accepted invasive intervention for ARAS in the large majority of patients in the United States is PTRAS. In contrast with the original reports, given advances in revascularization interventions, studies of angioplasty without stent placement are not included.

We included studies of any renal artery revascularization, with the caveats about concomitant aortic surgery noted above. We excluded studies that used endografts or endarterectomy that included the renal arteries to prevent or repair renal artery damage due to the aortic surgery.

We excluded "natural history" studies that did not evaluate a specific intervention, but instead followed patients regardless of treatment. This restriction is in contrast with the original reports.

Comparators of interest

Given the known paucity of comparative studies, we included both noncomparative (single group) studies and comparative studies that compared any of the three interventions of interest.

Outcomes of interest

With the TEP, we identified clinical and surrogate outcomes of greatest interest regarding the comparison of medical and revascularization interventions. It was agreed that given the chronicity of the disease process, only long-term clinical outcomes were of interest, along with adverse effects at any time. For the purposes of this report, "long-term" was defined as at least 6 months, but results at 12 months or more are of greater interest.

Outcomes of interest included:

- Mortality, all cause
- Kidney function
    - Event (e.g., need for renal replacement therapy [RRT])
    - Categorical (e.g., better/worse)
    - Continuous (i.e., GFR, creatinine clearance, serum creatinine [SCr])
- Blood pressure
    - Event (e.g., hypertensive crisis)
    - Categorical (e.g., better/worse)
    - Continuous BP
    - Medication need (e.g., number of antihypertensive drugs used)
    - ACEi or ARB tolerance
- CHF events, including flash pulmonary edema (including hospitalization)
- Other cardiovascular events (cardiac, cerebrovascular, peripheral vascular)
- Adverse events (e.g., postprocedure in-hospital or 30-day deaths, peri- and postprocedure events, drug reactions)

For questions 2 and 3, we also included subgroup and regression analyses that compared preintervention patient and intervention characteristics and outcomes of interest. These included, but were not limited to, patient demographics; clinical, imaging, laboratory, and anatomic characteristics of the RAS; and treatment variables, such as periprocedural medications, type of stent, use of distal protection devices, or other adjunct techniques. We extracted details from studies that reported analyses on the likelihood of outcomes based on the presence of patient or procedure related variables (e.g., that compared death rates among patients with high or low kidney function). We did not extract data related to comparisons of average values of the variables in patients with dichotomized outcomes (e.g., that reported mean age of those who lived and those who died). These latter analyses were not considered to be sufficiently helpful for a clinician making a decision of which intervention to recommend to a given patient.

When outcomes were reported at multiple time points, we included those that occurred at 6 months, 12 months, and each subsequent year, so long as there were at least 10 subjects being evaluated.

Years of intervention of interest

The original report restricted studies to those in which patients were treated after publication of the Fifth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-5) in 1993, when emphasis was placed on attempting to achieve lower BP levels than earlier sets of recommendations, together with recommendations for use of antilipid and antiplatelet treatments, and increasing use of ACEi and ARB. The current update maintains this time period for when patients were evaluated and treated.

Study designs of interest

The basic parameters were maintained for intervention-specific study design eligibility criteria are the same as in the previous report.

Comparative studies

For studies that compared two or more of the three intervention categories (medical therapy, PTRAS, surgical), we included studies of any study design, whether prospective or retrospective, as long as at least 10 subjects were evaluated in each group. Any comparative study that failed to meet eligibility criteria (e.g., angioplasty without stent versus comparator) was also examined to determine whether individual groups of subjects were eligible for review (e.g., the medical therapy arm).

Medical therapy only studies

For single-group medical intervention studies, we included only prospective studies of antihypertensive, antilipid, or antiplatelet medications with at least 10 subjects who received treatment.

Angioplasty with stenting studies

For single-group PTRAS studies, we included only prospective studies with at least 30 subjects who received treatment. The majority of available articles on ARAS have reported on groups of subjects who received PTRAS; therefore a higher sample size threshold was used.

Surgical revascularization studies

For single-group surgical studies, we included prospective or retrospective studies. We included prospective studies with at least 10 subjects who had surgery. Because there are relatively few prospective surgical studies, we also included retrospective studies with at least 100 subjects.

Case reports

To address the issue of patients excluded from essentially all comparative and almost all single group studies because they have acute decompensation (and, therefore, "require" revascularization), we included case reports and case series of patients with acute decompensation as defined by acute symptoms with acute worsening of kidney function, new-onset flash pulmonary edema, CHF, or peripheral edema, and/or recent-onset uncontrollable HTN. We selected the 20 most recently published eligible case reports, regardless of the intervention(s) employed.

Data extraction

Data extraction was conducted into customized forms in Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) designed to capture all elements relevant to the Key Questions. These included population characteristics, including description of patients' RAS, descriptions of the interventions analyzed, descriptions of relevant outcomes, enrolled and analyzed sample sizes, study design features, results (including adverse events), and risk of bias assessment. We captured methodological descriptions and results of subgroup or predictor (regression) analyses for any preintervention factor. Analyses based on postintervention factors (such as stent restenosis or followup BP) were excluded. When multiple models were reported, the most adjusted model was extracted. The forms were tested on several studies and revised as necessary.

All eligible studies from the original reports were entered into SRDR based on the original completed data extraction forms and, when necessary, the full-text articles.

Risk of bias assessment

We based the methodological quality of each study on predefined criteria. We used the Cochrane risk of bias tool for RCTs[10]—which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases—and selected questions from the Newcastle Ottawa Scale[11] about comparability of cohorts, representativeness of the population, and adjustment for different lengths of followup.

Data synthesis

All included studies were summarized in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, and results. Meta-analysis was considered, but given the large clinical and study design heterogeneity of the randomized and observational comparative studies (primarily in terms of indications for intervention) and the large heterogeneity in results of the single arm studies, meta-analysis was not deemed to be appropriate. Studies are summarized semiquantitatively and, for PTRAS and medical therapy studies, graphically.

The report uses the same basic structure as the original reports. Namely, it is organized by study design first (comparative studies, each of the single intervention analyses, and case reports), then by Key Question and outcome, within each study design section. Studies are summarized semiquantitatively and, for PTRAS and medical therapy studies, graphically.

Grading the strength of evidence

As per the AHRQ Methods Guide,[12] we assigned an overall grade describing the body of evidence for each key question that was based the number of studies, their study designs, the study limitations (i.e., risk of bias), the directness of the evidence to the Key Questions, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, other limitations, and the overall findings across studies. Based on these, we determined the strength of evidence as being high, moderate, or low, or there being insufficient evidence to estimate an effect. The grading was done by the team as a whole. RCTs and well-adjusted comparative observational studies were deemed to provide stronger evidence than poorly- or unadjusted comparative studies, which in turn provided stronger evidence than noncomparative studies. Issues related to the domains of study limitations, directness, consistency, reporting bias, and other limitations could decrease the strength of evidence, as described in the Methods Guide.

Peer review

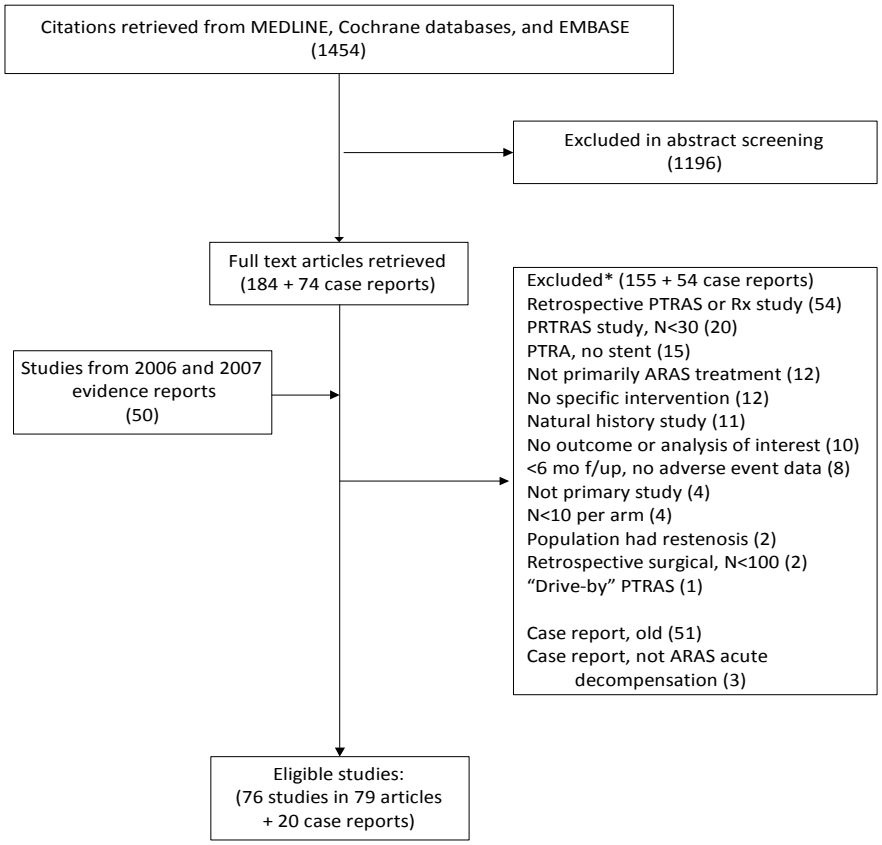
A draft version of this report [is being] reviewed by a panel of expert reviewers, including representatives from [pending] and the general public. The reviewers included experts in [pending]. These experts were either directly invited by the EPC or offered comments through a public review process. Revisions of the draft [will be] made, where appropriate, based on their comments. The draft and final reports [will] also reviewed by the Task Order Officer and an Associate Editor from another EPC. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

The literature search yielded 1454 citations (**Figure 2**). We identified 184 of these as potentially relevant full studies plus 74 case reports of potential interest. These were retrieved for further evaluation. We also rescreened the 50 studies included in the 2006 and 2007 reports to determine their eligibility for this update. Overall, 209 full-text articles and case reports did not meet eligibility criteria (see Appendix B for a list of rejected articles along with reasons for rejection); thus 76 studies (in 79 articles) are included in this report, and an additional 20 case reports were selected for inclusion.

Through the "grey literature" search for unpublished trials (to assess publication bias) in the FDA database, clinicaltrials.gov, the WHO International Clinical Trials Registry Platform, and conference proceedings, we did not find any trials with results that were not already included in the report.

Figure 2. Literature flow diagram



* Excluded list does not include studies that were screened and excluded for the 2006 report.

Comparative studies

We identified 18 studies (with a total of 2615 patients) that assessed the comparative effectiveness of treatment strategies for the treatment of ARAS and reported data on clinical outcomes.[13-30] Of these, 13 studies compared PTRAS with medical therapy,[13, 15-17, 20-26, 28, 29] five of which were RCTs;[15, 17, 24, 28, 29] one RCT compared surgical revascularization with medical

therapy only.[27] Four studies compared PTRAS with surgical therapy,[14, 18, 19, 30] one of which was a RCT.[14] The studies followed patients from 1 to 8 years.

PTRAS versus medical therapy

Key points

- 5 RCTs and 8 NRCSs compared PTRAS and medical therapy. Risk of bias concerns included unblinded outcome assessment, attrition bias, and selection bias and selective outcome reporting among the NRCSs. The RCTs were not representative of patients typically considering or undergoing PTRAS since both they and their clinicians had to have equipoise between PTRAS and continued medical therapy alone, which is sufficiently infrequent that recruitment into the trials was generally difficult. The NRCSs compared fundamentally different cohorts of patients—those for whom it was decided that PTRAS was indicated and those for whom PTRAS was not considered necessary (or an appropriate option). The NRCSs did not adequately adjust for the differences between patient cohorts.
- **Mortality**: 4 RCTs and 5 NRCS found no significant difference between interventions, but no study was adequately powered for mortality.
- **RRT**: 4 RCTs and 5 NRCSs had wide differences in rates of RRT across studies. Imprecise estimates found no significant differences in incident RRT between interventions.
- **Cardiovascular outcomes**: 3 RCTs and 3 NRCSs were heterogeneous in which outcomes were reported. No significant differences between interventions were found.
- **Pulmonary edema**: 3 RCTs reported on incident pulmonary edema or CHF. No differences between interventions were found.
- **Kidney function**: 5 RCTs and 5 NRCSs reported on changes in kidney function. Four of the RCTs found no significant differences in either likelihood of improvement (or worsening) of kidney function or measures of kidney function (GFR or SCr). In contrast, the NRCSs mostly found that patients's kidney function was more likely to improve (or less likely to worsen) after PTRAS than with medical therapy alone; however, these anlyses were not adjusted for underlying differences between the cohorts.
- **BP control**: 4 RCTs and 6 NRCSs reported on BP control. One RCT found no difference in improvement (or worsening) of BP control; one found that HTN was much more likely to be cured (PTRAS 11% vs. medical 0%), but similar percentages of patients had failure to improve (PTRAS 22% vs. medical 29%). All but one RCT found no significant difference in changes in measured BP. Two trials both found that patients on average were prescribed 0.2 fewer antihypertensive medications than those who remained on medical therapy only. The 6 NRCSs reported highly heterogeneous results, except that all but one found no difference in changes in number of antihypertensive medications.
- **Adverse events**: 5 RCTs and 4 NRCSs reported on adverse events, but only related to PTRAS. PTRAS-associated adverse events included periprocedural deaths (about 0.5%), angiography-related dissection and other vessel injuries, vessel occlusion, distal embolization, groin hematoma or hemorrhage, acute kidney injury, and stent dislocation.
- **Patient factors**: 3 RCTs reported on analyses of patient factors as predictors of outcomes. 2 RCTs found no factor that differentially predicted outcomes (between PTRAS and medical therapy); 1 RCT found that patients with flash pulmonary edema or with both rapidly declining kidney function and refractory HTN (prerandomization) had significantly better outcomes after PTRAS.

- **Treatment factors**: No comparative studies addressed differences in treatment factors as a predictor of outcomes in the comparison of PTRAS versus medical therapy.

Key Question 1.
Effects of intervention on outcomes

Randomized controlled trials (PTRAS vs. medical therapy)

Five RCTs compared PTRAS with medical therapy only.[15, 17, 24, 28, 29] The median mean age across the RCTs was 69 years. Enrolled patients had uncontrolled HTN while on two or more medications, with or without mild to moderate chronic kidney disease. About one-third of included patients had diabetes. Coronary artery disease among included patients ranged from 26 to 50 percent. Analyzed studies typically included more men (median 63% male) than women. The definitions of ARAS varied across studies, as described for each study, below (Appendix Tables C.1 and C.3). Half of these studies were of high or unclear risk of bias for blinding of outcome assessment or detection bias (2 high; 2 unclear), incomplete outcome data (attrition bias) (3 high; 1 unclear; 1 low), and sample representing the entire population (3 unclear, 2 low). In all studies the selective reporting bias was low (Appendix Table D.1).

The CORAL trial (Cooper 2014) was conducted at more than 100 international (>80% U.S.) medical centers that were vetted for their PTRAS experience and expertise.[17] Due to difficulties enrolling patients, the eligibility criteria changed during enrollment. Initially, eligible patients had SBP ≥155 mmHg on at least two antihypertensive medications and had >80 percent stenosis with a systolic pressure gradient ≥20 mmHg. Patients with stenosis as low as 60 percent who met other imaging criteria were also included. The threshold for SBP was subsequently removed, but if patients did not have systolic HTN, they had to have chronic kidney disease defined as GFR <60 mL/min per 1.73 m^2 not due a nonischemic cause. Patients were randomized to PTRAS with medical therapy or medical therapy alone, consisting of candesartan (an ARB) with or without hydrochlorothiazide (a diuretic), an amlodipine (calcium channel blocker)-atorvastatin (statin) combination pill, and antiplatelet therapy, all as tolerated. PTRAS was conducted with a distal protection device, and the Genesis™ stent was employed. Periprocedural prophylaxis was given with combination regimens of heparin with ticlopidine, clopidogrel, or aspirin. The trial was funded in part by government grants but many principal investigators disclosed industry connections. The trial analyzed 931 patients (90 percent power would have required 1080 patients). Overall, after a mean followup of 43 months, there were no significant differences in primary or secondary outcomes and no significant interactions were found in a predefined list of subgroups. PTRAS-related complications were rare and did not result in death or dialysis in any patient.

The ASTRAL trial (Wheatley 2009) was conducted in 57 hospitals primarily in the UK.[28] Patients with poorly controlled HTN or unexplained kidney disease were screened. Patients were enrolled if they had "substantial anatomical atherosclerotic stenosis…that was considered suitable" for PTRAS and "if the patient's doctor was uncertain that the patient would definitely have a worthwhile clinical benefit from revascularization." Almost all patients had at least 50 percent stenosis and 60 percent had at least 70 percent stenosis. Angioplasty without stenting was allowed but 95 percent had a stent. No distal protection devices were used. Only 83 percent of patients assigned to angioplasty had the procedure. Medical therapy varied according to local protocols, but "typically" consisted of "optimal blood pressure control," statins, and antiplatelet

drugs. The study was funded in part by industry. The study analyzed 806 patients (80 percent power was calculated to be achieved with 700 patients). Overall, during a median 34 month followup, no significant differences were found in the primary or secondary outcomes; however, the rate of progression of renal impairment, measured by the slope of 1/SCr was slower after PTRAS than with medical therapy alone (P=0.06). Serious complications associated with PTRAS occurred in 23 patients (6%), including cardiac death within 1 month, pulmonary edema, myocardial infarction, rehospitalization for hemorrhage, acute kidney injury, and peripheral amputations due to cholesterol embolisms.

The Bax 2009 trial was conducted in 10 medical centers in the Netherlands and France.[15] This study included 140 patients with GFR 15 to 80 mL/min per 1.73 m^2, 50 percent or greater stenosis, and controlled blood pressure on a stable medication dosage. Patients who had diabetes with proteinuria or malignant HTN were excluded. Patients were randomized to PTRAS with medical therapy or medical therapy alone, consisting of antihypertensive treatment (with a target blood pressure of <140/90 mmHg), a statin, and aspirin (and smoking cessation counseling). Multiple stents were used patients were given periprocedural aspirin. The trial was funded in part by industry. Overall, after 2 years of followup, no significant differences were found in primary or secondary outcomes between the two groups; however, only 46 of 64 patients (71%) assigned to PTRAS had the procedure (12 patients were found have stenosis <50 percent at angiography). Four of these 64 patients had serious procedure related complications including death and dialysis related to a cholesterol embolism.

The RASCAD trial (Marcantonio 2012) randomized 84 patients to PTRAS or medical therapy at a single institution in Italy.[24] The study enrolled patients who were undergoing nonemergent coronary angiography who were screened for ARAS by renal arteriography and who were found to have >50 percent and ≤80 percent stenosis, but not a single functioning kidney and elevated serum creatinine (>4 mg/dL) or an aortic aneurysm requiring surgery. All patients were treated with antihypertensive drugs, statins, and antiplatelet drugs. The study was funded by the hospital with no reported industry funding. The trial analyzed 84 patients who were followed for 1 year. Overall, there were no significant differences in primary or secondary outcomes. No serious PTRAS-related complications were reported.

The Ziakka 2008 trial was conducted in one institution in Greece.[29] They enrolled 82 patients with ARAS that was not specifically defined. Mean stenosis was 74 percent, using angiographic criteria, but no minimum criteria were reported. All patients had HTN. No medication regimen was specified, but patients were treated with different classes of drugs and "some of them" were taking statins. No mention is made of antiplatelet drugs. No funding sources was reported, but the authors declare no conflicts of interest. Patients were followed for a mean of 48 months. Compared to medical therapy alone, after PTRAS, significantly more patients had cure of HTN (DBP <90 mmHg off treatment, 11% vs. 0%) and improved kidney function (SCr decreased >20%, 31% vs. 0%), but similar numbers started dialysis. Other clinical outcomes were not reported. PTRAS-related complications were not reported.

Nonrandomized comparative studies (PTRAS vs. medical therapy)

Eight NRCSs compared PTRAS with medical therapy in a total of 1828 patients.[13, 16, 20-23, 25, 26] The average patient age was 70 years. All NRCSs included patients with uncontrolled HTN while on two or more medications, as well as those with or without mild to moderate CKD. Four studies included patients with decompensating conditions, such as acute flash pulmonary

edema and AKI.[21, 22, 25, 26] Between 30 and 80 percent of patients had coronary artery disease. NRCSs typically included more males (mean: 58% male) than females. See Appendix table C.3.

The definitions of RAS varied across NRCSs. Two included patients with over 50 percent stenosis,[22, 25] one with over 60 percent,[13] and three with over 70 percent stenosis.[20, 23, 26] ARAS was diagnosed in the preoperative period by renal angiography alone in two NRCSs,[21, 26] but was diagnosed using additional diagnostic methods, such as CT, MRI angiography or duplex ultrasonography, in the remaining six NRCSs. The median average SBP was 155 mmHg and DBP 82 mmHg. The median average GFR or CrCl in five NRCSs was 37.8 mL/min/1.73 m^2. See Appendix table C.1.

Two of eight NRCSs reported using bare-metal stents,[20, 22] but the remaining studies provided no information. Preprocedural and procedural prophylaxis against thrombosis was reported in four NRCSs with varying regimens: one used combination regimens of heparin with ticlopidine, clopidogrel, or aspirin;[22] two studies reported aspirin only;[21, 26] and one used heparin only.[23] The remaining studies provided no details of antiplatelet therapy. See Appendix table C.2.1.

These studies were evenly divided between high and low risk of bias for selection bias (4 high; 3 low), incomplete outcome data (attrition bias) (3 high; 1 unclear; 1 low), and selective reporting bias (3 unclear; 2 high; 2 low). In all studies except one, the sample representing the entire population was rated as having low risk of bias (6 low; 1 unclear) (Risk of Bias Description Appendix Table D.2).

Mortality (study duration 6 months or greater)

Randomized trials

No study was reported to be adequately powered to detect a difference between interventions for mortality. See Appendix Table C.4.1.

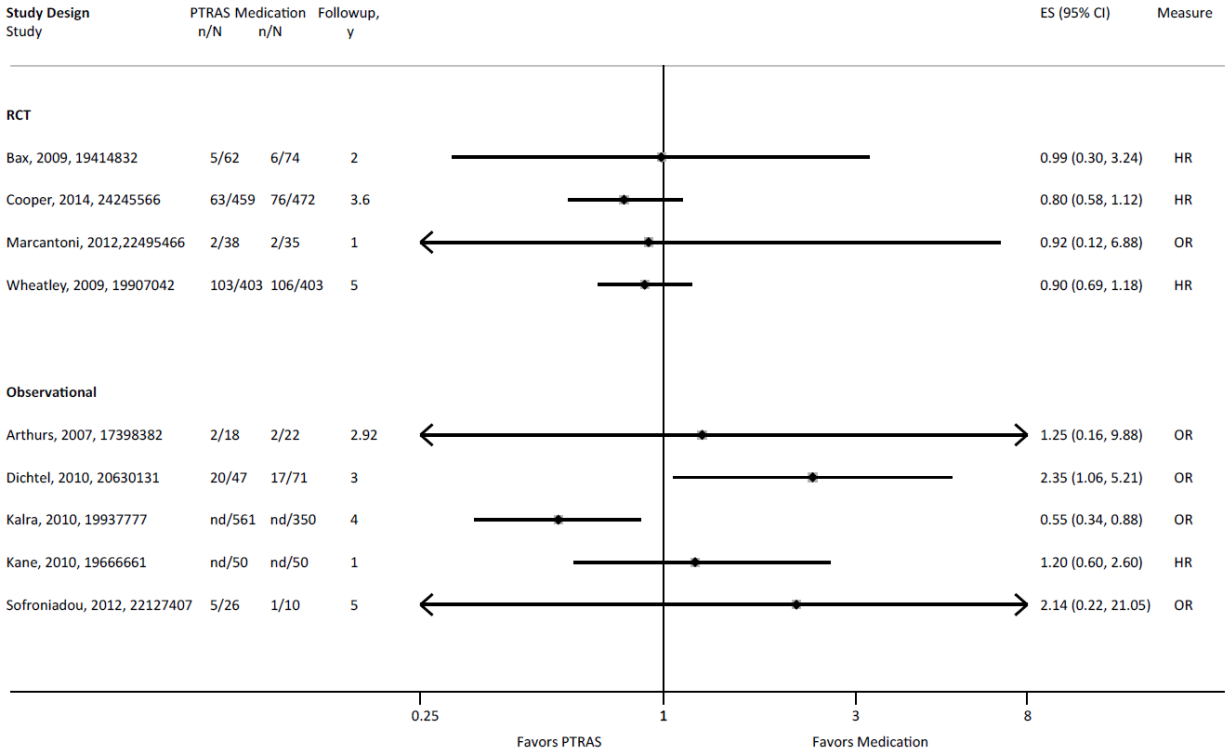
Four RCTs reported mortality data for 1 to 5 years followup duration (**Figure 3**).[15, 17, 24, 28] The number and time frame of deaths were similar in all four RCTs. Bax 2009 found no difference in all-cause death (crude HR 0.99 [0.30, 3.24]) and cardiovascular death (crude HR 0.59 [0.11, 3.25]) after 2 years between 62 patients who received PTRAS intervention and 74 who were treated medically.[15] Similarly, no difference results were found in the CORAL trial for the outcomes of all-cause death (adjusted HR 0.80 [0.58–1.12]), cardiovascular death (adjusted HR 0.89 [0.58–1.36]), and death due to renal causes (adjusted HR 1.89 [0.17–20.85]) after 3.6 years between the 459 patients who received PTRAS intervention and the 472 who were treated medically. In this RCT, there was no difference in mortality by Kaplan-Meier curve analysis up to 5 years after either PTRAS (n=459) or of medical therapy (n=472).[17] Of the 806 patients who were enrolled in the ASTRAL trial, 103 in the PTRAS group and 106 in the medical-therapy group died during the 5-year study period (HR 0.90 [0.69–1.18]).[28] In the RASCAD trial, there was no significant difference between two comparison groups (2 deaths occurred in both arms; OR 0.92 [0.12, 6.88]).[24]

Nonrandomized studies

Five NRCSs comparing PTRAS with medical therapy reported mortality data, and none found a statistically significant difference in all-cause death (**Figure 3**).[13, 20, 22, 23, 26] No study was reported to be adequately powered to assess mortality. Only one NRCS provided adjusted analysis, having matched patients for age and sex;[23] none of the studies conducted propensity

score matched analyses. Effect sizes ranged from 0.55 to 2.35, with no clear explanation for the heterogeneity. See Appendix Table C.4.1.

Figure 3. Death: PTRAS versus medical therapy alone



Point estimates of odds ratios (OR) or hazard ratio (HR) and 95% confidence intervals from individual studies. ES = effect size, n/N = number of events/total, nd = no data, PTRAS = percutaneous transluminal renal angioplasty with stent placement, RCT = randomized controlled trials.

Renal replacement therapy

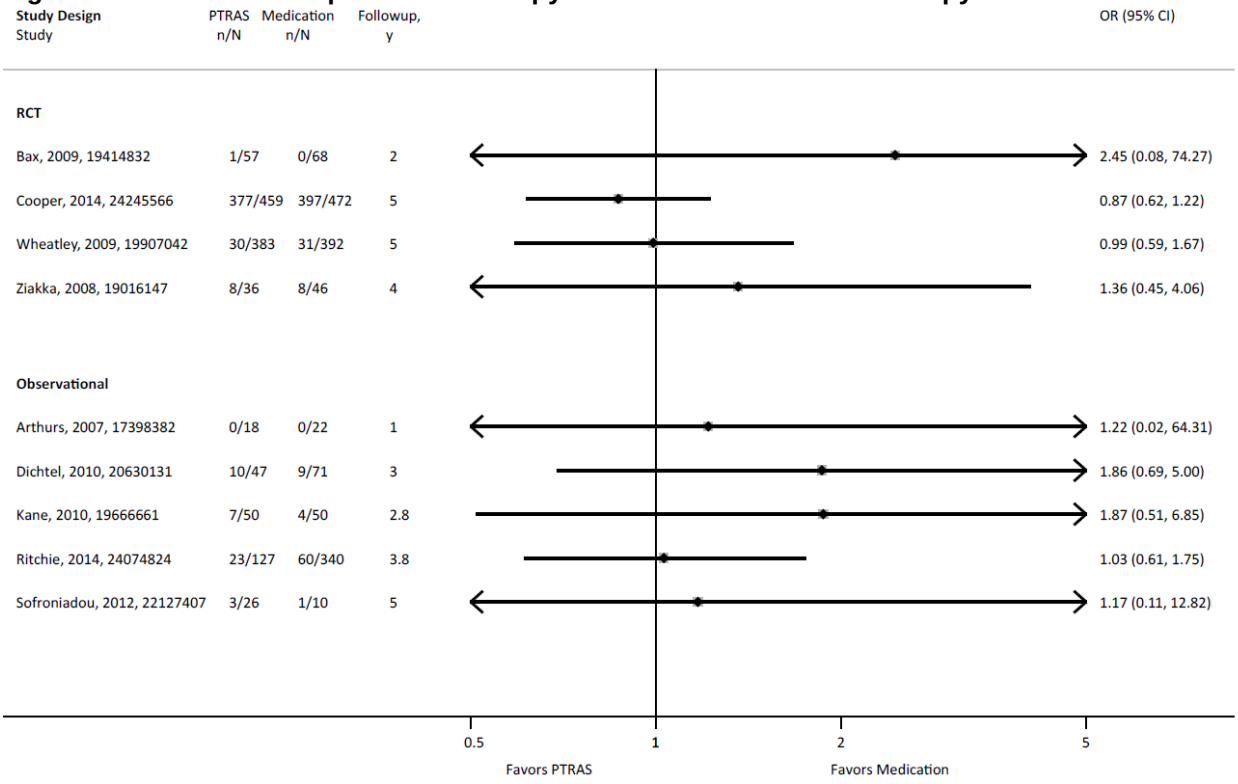
Randomized trials

Four of the RCTs reported on RRT.[15, 17, 28, 29] The overall rates of dialysis varied from 0.7 percent at 2 years to 10 percent at a mean of 4 years of followup (**Figure 4**). However, no statistically significant differences were found between PTRAS and medical therapy for all trials, with ORs ranging from 1.0 to 2.0, with wide confidence intervals. See Appendix Table C.4.6.

Nonrandomized studies

Five studies reported data on patients progressing to end stage renal disease (ESRD) (**Figure 4**).[13, 20, 23, 25, 26] One study explicitly reported that no patients started dialysis. In the remaining four studies, for patients progressing to ESRD, three found no statistically significant difference between comparison groups, with ORs ranging from 1.03 to 7.94 and wide confidence intervals, across all studies. No analysis was adjusted for baseline differences or patient characteristics. See Appendix Table C.4.6.

Figure 4. Incident renal replacement therapy: PTRAS versus medical therapy alone



Point estimates of odds ratios (OR) and 95% confidence intervals from individual studies. n/N = number of events/total, PTRAS = percutaneous transluminal renal angioplasty with stent placement, RCT = randomized controlled trials.

Cardiovascular outcomes

Randomized trials

Three RCTs[15, 17, 28] reported similar cardiovascular event rates in both treatment groups, including MI; stroke; newly diagnosed coronary artery, peripheral artery, or cerebrovascular disease; and cardiovascular mortality. See Appendix Table C.4.12.

Nonrandomized studies

Three NRCSs[13, 23, 26] reported on different cardiovascular outcomes in each study. Stroke, angina, and abdominal aortic aneurysm rupture each occurred in no or one patient per study. In one study, myocardial infarctions occurred in 17 percent of patients 2 years after PTRAS and 4.5 percent of patients who remained on medical therapy alone, yielding a nonsignificant unadjusted hazard ratio of 3.0 (0.60, 14). In a second study, 14 percent of patients required coronary revascularization within a mean of 2.8 years after PTRAS compared with 22 percent in the medical therapy group (unadjusted OR = 0.58 [0.20, 1.64]). See Appendix Table C.4.16.

Pulmonary edema

In three RCTs (Bax, CORAL, Marcantonio),[15, 17, 24] episodes of pulmonary edema or CHF were uncommon (1% to 6%) and did not significantly differ between treatment groups. See Appendix Tables C.4.16 and C.4.17. None of the NRCSs reported on pulmonary edema.

Kidney function

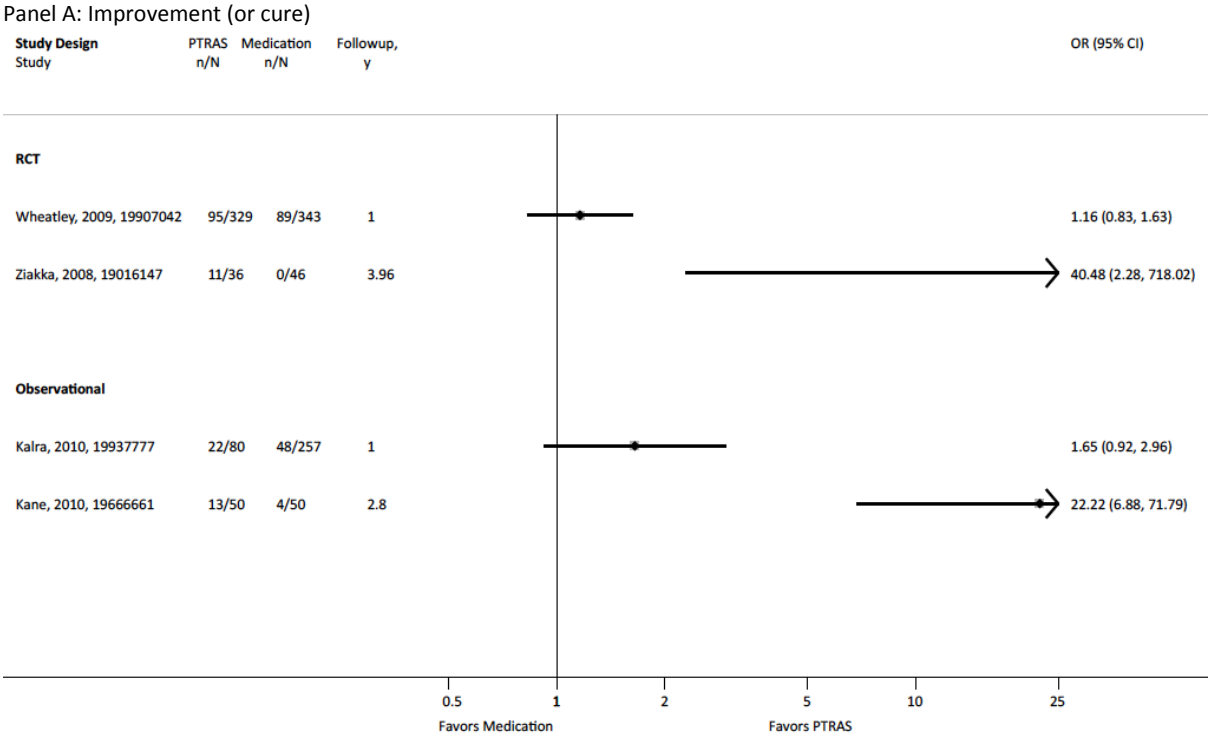
Randomized trials

All five RCTs reported on changes in kidney function.[15, 17, 24, 28, 29] No differences were found in the CORAL trial for the outcomes of progressive renal insufficiency (adjusted HR 0.86 [0.64–1.17]).[17] In the ASTRAL trial, the two study groups had similar rates of renal events (HR 0.97 [0.67-1.40]).[28] In Marcantonio 2012, GFR remained stable for 1 year in both treatment arms and no significant difference was found.[24] Bax 2009 found no significant difference in SCr or creatinine clearance at 2 years.[15] Only in Ziakka 2008 was a significant difference found; kidney function improved (SCr decreased >20 percent) in 30.5 percent or patients and worsened (SCr increased >20 percent) in 36.2 percent of patients in PTRAS arm, whereas in the medical therapy arm kidney function remained stable in 69.8 percent of patients and worsened in 30.2 percent (P<0.001) (**Figure 5**).[29] See Appendix Tables C.4.2, C.4.3, C.4.5, C.4.6, and C.4.7.

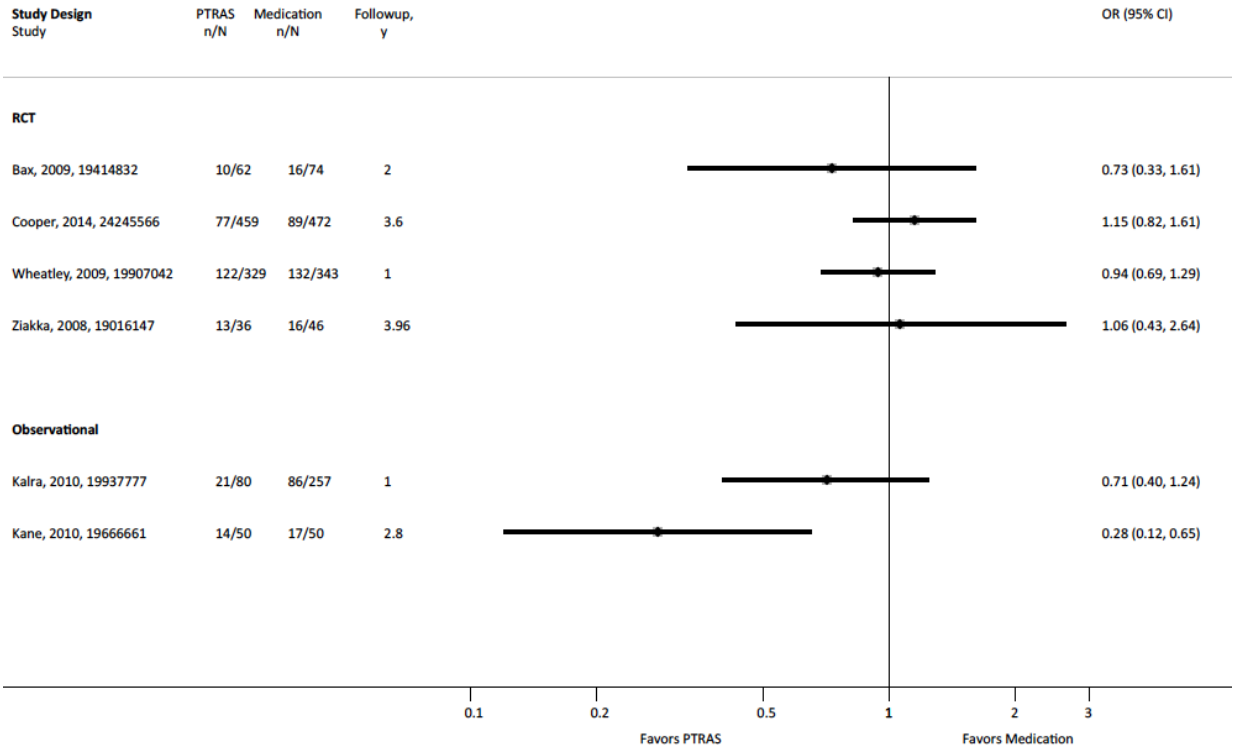
Nonrandomized studies

Three NRCSs reported ordinal outcomes for renal improvement (**Figure 5, above**).[21-23] Kidney function improved in 7 to 25 percent of patients in PTRAS group, as compared with 6 to 8 percent improvement in the medical therapy alone group. Five NRCSs reported higher GFR in the PTRAS group, as compared with the medical therapy group in kidney function.[20-23, 26] These studies reported a median 0.1 mL/min change in GFR in PTRAS, as compared with a median -0.4 mL/min change in GFR in medical therapy only group. See Appendix Tables C.4.2, C.4.3, C.4.5, C.4.6, and C.4.7.

Figure 5. Kidney function improvement (panel A) and worsening (panel B): PTRAS versus medical therapy alone



Panel B: Worsening



Point estimates of odds ratios (OR) and 95% confidence intervals from individual studies. n/N = number of events/total, PTRAS = percutaneous transluminal renal angioplasty with stent placement, RCT = randomized controlled trials.

Blood pressure control

Randomized trials

Bax 2009 and Ziakka 2008 reported BP related events (as categorical/ordinal outcomes).[15, 29] In Bax 2009, refractory HTN continued in 0 percent in the PTRAS arm, as compared with 4 percent in medical therapy alone;[15] the percentage of patients with target BP (<140/90 mmHg) was similar in both arms (32% vs. 29%, P=0.95). In Ziakka 2008, BP was cured in 11.1 percent, improved in 66.6 percent, and failed to improve in 22.3 percent of patients in PTRAS arm, whereas in the medical therapy arm HTN was cured in 0 percent of patients, improved in 71.4 percent, and failed to improve in 28.6 percent (P<0.001).[29] See Appendix tables C.4.12 and C.4.13.

Across the four RCTs[15, 17, 24, 28] comparing PTRAS versus medical therapy, there was a reduction in SBP that ranged from −6 to −17 mmHg in PTRAS arms, as compared with a range of −5.5 to −16 mmHg reduction in SBP in the medical therapy arms. In their longitudinal analysis, the CORAL trial reported a significant difference in SBP favoring PTRAS (−2.3 mm Hg; 95% CI, −4.4 to −0.2; P = 0.03), as compared with medical therapy.[17] In contrast, the other three trials (ASTRAL, RASCAD, Bax 2009)[15, 24, 28] found no significant between-group difference in SBP or DBP. The CORAL trial did not report data on DBP (**Figure 6**). See Appendix Tables C.4.8, C.4.9, and C.4.11.

Changes in number of antihypertensive medications were reported for the CORAL and ASTRAL trials.[17, 28] Both found that after PTRAS, patients on average were prescribed 0.2 fewer antihypertensive medications than those who remained on medical therapy only; this difference

was statistically significant in CORAL (difference = −0.2 [−0.397, −0.003], P=0.046), but untested (no confidence intervals reported) in ASTRAL (Appendix Table C.4.13).

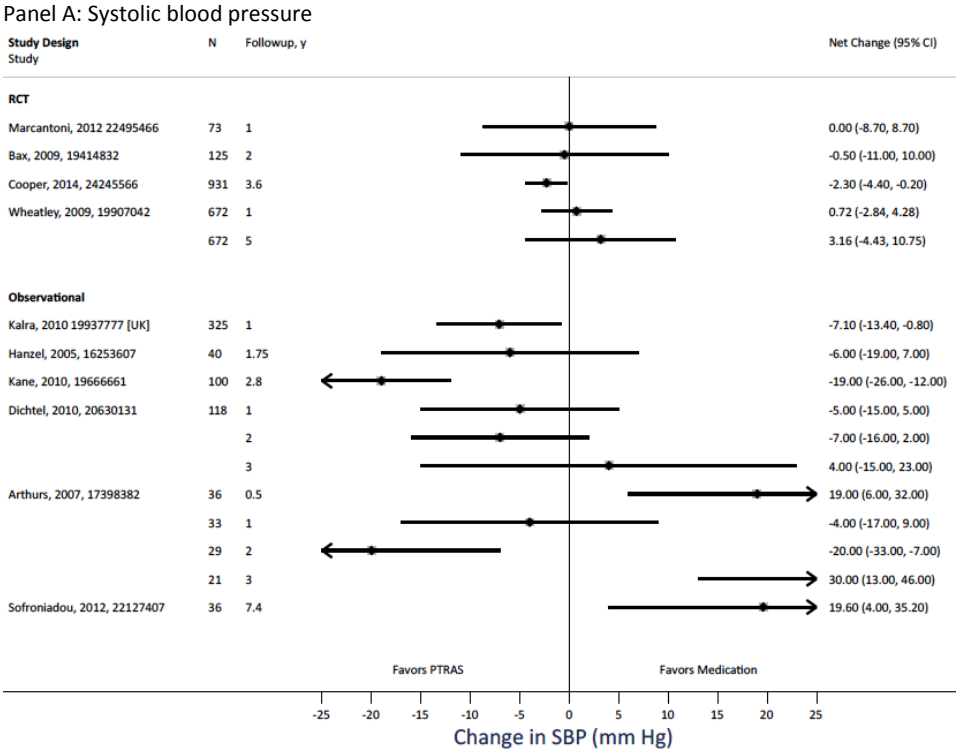
Nonrandomized studies

Two NRCSs reported ordinal outcomes for BP improvement.[19,21] There were no significant differences in these results: BP was cured in 18 percent and improved in 40 percent of PTRAS patients versus 20 percent and 33.3 percent, respectively, in medical therapy alone.[19] Both groups observed a significant decrease in BP, but the magnitude of effect was greater in the PTRAS, as compared with medical therapy (9% SBP decrease in PTRAS vs. 5% decrease in medical therapy only; p=0.016).[21] See Appendix table C.4.13.

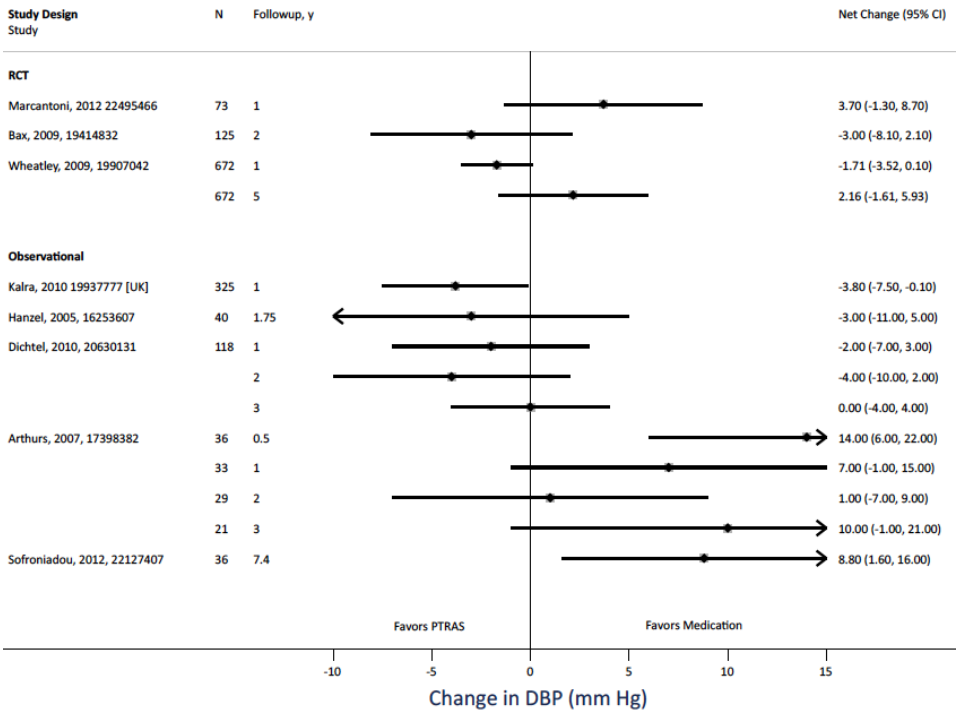
The six NRCTs that reported on changes in blood pressure were highly heterogeneous (**Figure 6, above**). Two studies (Kalra 2010 and Kane 2010) found statistically significant net reductions in SBP favoring PTRAS by 7 or 19 mmHg, and, in Kalra 2010, significant net reduction in DBP also favoring PTRAS by 4 mmHg (Kane 2010 did not report DBP). But Sofroniadou 2010 found significantly higher SBP (20 mmHg) and DBP (9 mmHg) in patients who had PTRAS. Two studies (Hanzel 2005 and Dichtel 2010) found no significant difference for either SBP or DBP. Arthurs reported data that allowed calculations of net change BP, with highly variable differences between PTRAS and medical therapy at different time points from 6 months to 4 years (4 year data omitted from figure because sample size appeared to be about 4 or 5 individuals in each group at that time point). See Appendix Tables C.4.8, C.4.9, C.4.11.

Changes in number of antihypertensive medications were reported five NRCSs. [13, 20, 21, 23, 26] Only one[23] reported a statistically significant difference between groups. See Appendix Table C.4.13.

Figure 6. Blood pressure, net change: PTRAS versus medical therapy alone



Panel B: Diastolic blood pressure



Point estimates of net change blood pressure and 95% confidence intervals from individual studies. PTRAS = percutaneous transluminal renal angioplasty with stent placement, RCT = randomized controlled trials.

Adverse events (including 30-day mortality)

Randomized trials

Five trials reported on adverse events related to PTRAS; adverse events related to medications were not reported.[14, 15, 17, 24, 28] Two trials reported that 2/280 (0.7%)[28] and 2/64 (3%)[15] died within 30 days of the procedure due to complications following renal artery perforation or cardiac events. CORAL, the largest trial, had no periprocedural deaths.[17] Across all four trials 4 of 848 patients who received PTRAS (including those assigned to medical therapy who crossed over to receive PTRAS) died (0.5%). Of note, the CORAL trial reported that 1 of 478 patients assigned to medical therapy had a fatal stroke on the day of randomization.[17] Other serious adverse events reported included, in CORAL, only angiographic complications (implicitly without long-term consequence) including dissections (11/495, 2.2%), vessel occlusions (6/495, 1.2%), distal embolization (6/495, 1.2%), and in one patient each, wire perforation, vessel rupture, and pseudoaneurysm.[17] In ASTRAL, 12 serious events in 11 patients occurred in 280 patients, including four with groin hematomas or hemorrhages requiring hospitalization, five with clinically significant acute kidney injury, and one with renal-artery occlusion.[28] In addition to the procedure-related deaths, Bax 2009 reported two patients with femoral artery false aneurysms and one patient who eventually required permanent dialysis after cholesterol embolization.[15] The only serious adverse event in Marcantonio 2012 was that 1/41 patients (2.5%) required a blood transfusion and rehospitalization from a groin hematoma.[24] Balzer 2009 reported 5 periprocedural events in 49 patients, including stent dislocation, local dissection, and postoperative occlusion.[14] Appendix Tables C.4.18 and C.4.19.

Nonrandomized studies

Four NRCSs reported periprocedural complications.[13, 21, 25, 26] No study reported on medication-related adverse events. Three reported no major complications (renal failure or death in one study;[21] acute thrombosis, dissection, renal failure, rapid kidney function decline, hemorrhage, or death in one study;[13] undefined in one study).[26] In contrast, Ritchie 2014 reported a 4.8 percent major complication rate (undefined).[25] See Appendix Tables C.4.18 and C.4.19.

Key Question 2.
Association of patient factors with outcomes

The CORAL trial tested for interaction terms with their composite outcome (cardiovascular or renal death, stroke, myocardial infarction, CHF hospitalization, GFR decrease by at least 30%, or RRT).[17] None of the prespecified terms (sex, black race, global kidney ischemia, or diabetes) interacted with (altered the comparative effect between) the interventions (PTRAS versus medical therapy alone). They also found no interactions with other tested factors—SCr >1.6 mg/dL, GFR <45 mL/min, SBP >160 mmHg, age >70 years, or renal artery stenosis ≥80 percent.

In the ASTRAL trial, subgroup analyses were performed for the analysis of the slope of 1/SCr (a proxy for GFR) over 5 years.[28] No differences in effect were reported among the prespecified subgroups (baseline SCr and GFR, percent stenosis, kidney length, and prior renal impairment progression) or bilateral versus unilateral severe (>70%) stenosis.

Ritchie 2014, in a retrospective observational study that compared PTRAS to medical therapy only, ran analyses adjusted for age, sex, kidney function, proteinuria, BP, renal artery patency, diabetes, and use of ACEi/ARB in different subgroups of patients, comparing PTRAS and medical therapy.[25] In patients presenting with flash pulmonary edema, those who received PTRAS had a reduced relative rate of death (0.36; 95% CI 0.16, 0.80) compared with those treated medically. Similarly, those presenting with both rapidly declining kidney function (SCr increased 20% or by 1.14 mg/dL in 6 months) and refractory HTN (BP >140/90 mmHg on at least three medications) who received PTRAS had a reduced relative rate of death (0.14; 95% CI 0.01, 0.99) compared with those treated medically. In contrast, those who presented with either rapidly declining kidney function or refractory HTN alone had statistically similar rates of death regardless of treatment choice. In all risk groups, rates of cardiovascular events and RRT were similar between those who received PTRAS or medical therapy.

Key Question 3.
Association of treatment factors with outcomes

No comparative study addressed this question.

Surgery versus medical therapy

One RCT (but no NRCS) compared open surgical revascularization with medical therapy alone.

Key points

- 1 RCT only compared surgery and medical therapy. The study low (or unclear) risk of bias.
- **Outcomes**: No significant differences were found between interventions for death, dialysis-free survival, or BP control. Adverse events were not reported.
- **Patient factors**: Patients with baseline azotemia had better outcomes if surgically revascularized, in contrast with the total cohort, but no significant interactions were found.
- **Treatment factors**: No comparative studies addressed differences in treatment factors as a predictor of outcomes in the comparison of surgery versus medical therapy.

Key Question 1.
Effects of intervention on outcomes

Randomized controlled trial (surgery vs. medical therapy)

Uzzo 2002 randomized 52 patients with bilateral ARAS (or ARAS in a solitary kidney) or unilateral disease with chronic kidney disease (SCR >1.5 mg/dL or GFR <70 mL/min).[27] Patients had >75 percent stenosis. Excluded were patients with SCr >4.0 mg/dL, DBP >100 despite "adequate medical management" or comorbid conditions precluding surgical revascularization. Medical management was not described (but was under the direction of a single nephrologist). Surgery included aortorenal bypass (6/25 patients), splenorenal bypass (3/25), hepatorenal bypass (8/25), ileorenal bypass (6/25), endarterectomy (1/25), and aortic replacement with renal artery reimplantaion (1/25). See Appendix Tables C.1, C.2.2, C.3).

This RCT was rated as having low risk of bias for outcome assessment (detection bias), attrition bias, and selective reporting (reporting bias). For all other items, including detection bias and sample representativeness of the entire population, it was unclear. See Appendix Table D1.

Median follow-up time was 74 months. Overall, there were no significant differences in outcomes or times to outcomes, including death (approximately 60% at 7 years in both groups, P=0.31), time to death (surgery 69 months vs. medical 62 months; P=0.75), dialysis-free survival (P=0.64), or BP control (undefined, P=0.20). See Appendix Tables C.4.1, C.4.6, C.4.12.

Adverse events were not reported.

Key Question 2.
Association of patient factors with outcomes

Uzzo 2002 reported that patients with baseline azotemia (SCr 2 to 4 mg/dL) were less likely to die or have uncontrollable HTN if surgically revascularized than if treated medically (P=0.11),[27] in contrast with no significant difference in effect for the total cohort, who also included patients without azotemia. However, by multivariable analysis, no interactions were found between treatment choice and baseline demographic factors.

Key Question 3.
Association of treatment factors with outcomes

No comparative study addressed this question.

Surgery versus PTRAS

One RCT and three NRCSs compared surgery to PTRAS.

Key points

- 1 RCT and 3 NRCSs compared surgery and PTRAS. The RCT was of low (or unclear) risk of bias. The NRCSs suffered from selection and attrition biases; they also did not adjust their analyses for differences between patient cohorts.
- **Outcomes**: The RCT found no difference in death, change in kidney function (SCr), BP, or antihypertensive treatment requirement. Periprocedural adverse events occurred in both groups. 2 of the 3 NRCSs reported only limited data, reporting no differences in mortality or HTN. 1 NRCS found similar rates of death and RRT, long-term kidney function, and BP control; perioperative complications were significantly more common with open surgery than with PTRAS.
- **Patient factors**: 1 of 2 studies found that patients with HTN as their indication for intervention were more likely to have better outcomes with surgery than PTRAS, but patients with renal salvage as their indication had similar outcomes regardless of revascularization approach; but the interaction between subgroups and interventions was not analyzed. The second study found similar associations between renal resistive index and mortality regardless of revascularization approach.
- **Treatment factors**: No comparative studies addressed differences in treatment factors as a predictor of outcomes in the comparison of surgery versus PTRAS.

Key Question 1.
Effects of intervention on outcomes

Randomized controlled trial (surgery vs. PTRAS)

Balzer 2009 randomized patients with >70 percent ostial ARAS with HTN to either surgical revascularization (thromboendarterectomy or aortorenal bypass) or angioplasty (with or without stent).[14] In 27 patients, thromboendarterectomy was performed in 45 renal arteries and aortorenal bypass grafting in four renal arteries. In the 22 patients who had angioplasty, stents were placed in 22 of 28 renal arteries receiving treatment. Among the patients, 63 percent were male, mean age was 64 years, 18 percent had diabetes, 78 percent hyperlipidemia, and 53 percent coronary artery disease. Notably, 60 percent of patients who had surgical revascularization had >20 pack-years of smoking history, in contrast with 9 percent of those who had PTRAS; analyses were not adjusted for this baseline difference.[14] See Appendix C.1, C.2.3, C.3.

This RCT was rated as having low risk of bias for attrition bias and selective reporting (reporting bias). For all other items, including sample representativeness of the entire population, selection bias, performance bias, and detection bias, it was unclear. See Appendix D.1.

During a mean 54 months of follow-up, deaths were not statistically significantly different (surgery 26% vs. PTRAS 18%, P=0.80) (Appendix C.4.1). RRT or cardiovascular events were not reported. Four years after surgery, SCr levels stabilized after surgery, and there was a significant improvement in PTRAS compared to baseline levels (P=0.04). However, there was no difference between groups (Appendix C.4.2, C.4.4, C.4.5). Also at 4 years, there was significant improvement in SBP and DBP in both groups compared to baseline levels, but the difference was not significant between the two groups (P=0.73 for SBP and P=0.49 for DBP) (Appendix C.4.8, C.4.10, C.4.11).[14] This RCT also reported ordinal outcomes for BP improvement or cure and found no difference between groups (P=0.72) (Appendix C.4.13). Two patients in each group no longer required antihypertensive treatment to control their HTN. There were no periprocedural deaths. After surgery, one patient required PTRAS due to local dissection after endarterectomy. After PTRAS, two patients required surgery due to dislocated stents (Appendix C.4.19)

Nonrandomized comparative studies (surgery vs. PTRAS)

Three retrospective NRCSs compared patients who had open surgery and those who had PTRAS.[18, 19, 30] The studies were of unclear or high risk of bias for selection bias regarding the similarity of the compared groups. Two of the studies were of high risk of bias for incomplete outcome data (attrition bias) (Risk of Bias Description Appendix Table D.2).

In de Donato 2007, [19] patients were included with ≥80 percent stenosis and HTN requiring at least three medications. Of note, 15 percent of patients had FMD. Patients had a mean age of 62 years, and 81 percent were male. The study included 83 patients who had 97 renal arteries treated. It was not reported how many patients received each intervention, but 15 renal arteries had surgical revascularization (11 endarterectomy, 4 aortorenal bypass) and 82 arteries had angioplasty (68, 81% with stent). There were no major periprocedural complications (including death) with either procedure. After 1 year, there was no significant difference in whether patients had HTN improvement or cure (however, this was analyzed by renal artery not patient). No other outcomes were compared between interventions. See Appendix Tables C.1, C.2.3, C.3, C.4.19; Risk of bias D.2.

In Crutchley 2009, 56 patients had surgical revascularization because they had HTN requiring multiple medications, a history of flash pulmonary edema or malignant HTN, or ischemic nephropathy (not defined) with bilateral disease or a solitary kidney. Among these patients, 17 had bypass, 22 had endarterectomy, and 17 had combined aortic and renal artery procedures. In contrast, 30 patients had angioplasty (26, 87% with stent) for a variety of unreported reasons. Patients' mean age was 68 years and 46 percent were male. No outcome of interest was explicitly compared between interventions, but the article implied no significant difference in mortality during a mean of 58 months of followup.[18] See Appendix Tables C.1, C.2.3, C.3, C.4.1; Risk of bias D.2.

Patel 2009 retrospectively compared 203 patients who had PTRAS and 47 who had open surgery for ARAS with at least 75 percent stenosis.[30] Patients were excluded if renal artery revascularization was conducted in the context of concomitant aortic reconstruction without specific indications for renal artery revascularization, but one-third (15/47) did have concomitant aortic surgery. Among the open surgeries, 21 (47%) were endarterectomies and 26 (53%) were bypasses, of which 17 were aortorenal, 6 were hepatorenal, 2 were splenorenal, and 1 was iliorenal. Few details were reported regarding the PTRAS procedures. Patients' mean age was 71 years, and 58 percent were men. Fifty-one percent had "chronic renal insufficiency," 13 percent

acute renal failure, and for 49 percent the reason for the intervention was renal salvage. Almost all patients (94%) had HTN, and for 51 percent this was the indication for the intervention. All-cause death (28% at 3 years) and incident RRT (~30% at 3 years) rates were similar between groups (P=0.9 and 0.7, respectively) across 3 years. At 1 year, statistically significantly more patients had improved kidney function after open surgery than PTRAS (52% vs. 24%, P=0.009); this difference persisted beyond 1 year but was not statistically significant (43% vs. 19%, P=0.1). At all time points, nonsignificantly more patients had cure or improvement in blood pressure control (e.g., open 89% vs. PTRAS 74% at 1 year, P=0.2). SCr, SBP, and DBP were all similar at and after 1 year of followup (P>0.6). Perioperative complications were significantly more common with open surgery (23%) than with PTRAS (12%, P=0.001), including death (1/47 vs. 1/203).

Key Question 2.
Association of patient factors with outcomes

Crutchley 2009 found that a renal resistive index ≥0.8 (vs. <0.8) predicted all-cause mortality among patients who had PTRAS (HR 5.7, 95% CI 1.1-28) or surgical revascularization (HR 4.8, 95% CI 1.6-14).[18] However, no statistical analysis of an interaction between renal resistive index and revascularization approach was reported.

Patel 2009 found that patients with HTN as their indication for intervention were significantly more likely to have blood pressure control cure or improvement and kidney function improvement at 1 year after open surgery than PTRAS patients (100% vs. 73%, P=0.04; 50% vs. 8%, P=0.01, respectively), but no significant differences by intervention if renal salvage was their indication.[30] However, the differences in effects between indication subgroups and revascularization approach were not statistically analyzed.

Key Question 3.
Association of treatment factors with outcomes

No comparative study addressed this question.

Single-group studies

Eligibility criteria for single-group studies varied based on the expected volume of evidence for each intervention. For PTRAS, we include prospective studies with at least 100 patients. For medical therapy, we include prospective studies with at least 10 patients. For surgery, we include both prospective studies with at least 10 patients and retrospective studies with at least 100 patients. These studies include both true single-group studies (in which the whole study comprised a cohort of patients receiving a single intervention), comparisons of different cohorts of patients all receiving the same overarching intervention (PTRAS, medical therapy alone, or surgery), and relevant cohorts from RCTs and NRCSs. Note that not all cohorts from the comparative studies are included here. For example, the single groups from a retrospective comparison of PTRAS versus medical therapy do not meet criteria for analysis of single-group studies.

Angioplasty with stenting

Key points

- 67 cohorts of patients (in 63 prospective studies) reported outcomes after PTRAS. The studies were highly heterogeneous in both their included patients, indications for PTRAS, and specific PTRAS techniques. Many of the studies were deemed to be at high risk of bias for failure to adjust for different lengths of followup, attrition bias, and selective outcome reporting.
- **Mortality**: In 31 studies, mortality ranged from 0 to 53 percent after 6 months to 5 years of followup (one study reported at 15 years). Other than a general trend toward increased death with longer-term followup, there was no clear explanation across studies for the difference in mortality.
- **RRT**: In 7 studies, incident RRT occurred in 2.3 to 23 percent of patients between 1.25 and 5 years, but with no clear explanation of the heterogeneity across studies, including length of followup.
- **Cardiovascular outcomes**: In 12 studies, various cardiovascular outcomes were reported to occur, but with highly heterogeneous percentages of patients (including CHF 0-83%, MI 1-82%, stroke 1-19%).
- **Kidney function**: In 4 studies 2 to 82 percent of patients had episodes of acute kidney injury. In 21 studies, kidney function improved in 12 to 82 percent and worsened in 4 to 37 percent of patients. 21 studies had a median change in GFR of 0 mL/min (range -9 to 10 mL/mL). There was no clear explanation across studies for the wide heterogeneity in change in kidney function.
- **BP control**: In 2 studies 0 and 4 percent of patients had new-onset HTN. In 19 studies, BP improved in 4 to 69 percent and stabilized or worsened in 7 to 67 percent of patients. In 36 studies, median changes in systolic BP were -17 mmHg (range -51 to 28) and in diastolic BP were -6 mmHg (range -30 to 5). In 30 studies, the median change in number of antihypertensive medications was -0.3 (-1.4 to 1.2). There was no clear explanation across studies for the wide heterogeneity in change in BP control.
- **Adverse events**: In 19 studies, adverse events included post-operative death, RRT, and acute renal failure; and severe bleeding, dissection, unplanned surgery, and thrombosis.
- **Patient factors**: 20 studies reported on analyses of patient factors as predictors of outcomes after PTRAS. Overall, the studies were heterogeneous in their analyses and findings. Among predictors analyzed by at least 3 studies, those with some indication of an association with favorable *kidney and BP* outcomes included *worse* pre-PTRAS kidney function (in 6 of 13 studies), bilateral stenosis (in 3 of 9 studies), *higher* pre-PTRAS BP (in 3 of 5 studies), *higher* grade of stenosis (in 2 of 5 studies). *Absence* of cardiovascular disease, female sex, and *younger* age were found to be significantly associated with better outcomes in only 1 of 4 or 5 studies. However, in contradistinction to their associations with intermediate outcomes, death, RRT, and composite clinical outcomes were associated with *worse* pre-PTRAS kidney function (in 3 of 5 studies), bilateral stenosis (in 2 of 5 studies), cardiovascular disease (in 2 of 4 studies), and CHF (in 3 of 5 studies). In addition, smoking and diabetes were associated with clinical events in only 1 of either 3 or 4 studies.
- **Treatment factors**: 3 studies addressed differences in treatment factors as predictors of outcomes. No differences in outcomes were found with or without gold-coated stents, sirolimus eluting stents, embolic protection devices, or intraluminal brachytherapy.

Key Question 1.
Effects of intervention on outcomes

In 63 articles,[14-17, 19, 21, 22, 24-26, 28, 29, 31-81] we identified 67 cohorts of patients who were treated with PTRAS (a total of 8,286 patients) in prospective studies. Among the studies, 48 cohorts[33-37, 39-58, 62-67, 69-74, 76-80] assessed the effectiveness of PTRAS on outcomes in single cohorts of patients (or compared different cohorts of patients receiving PTRAS), and 19 cohorts[14-17, 19, 21, 22, 24-26, 28, 29, 38, 59-61, 68, 75] were from studies comparing PTRAS to medical therapy or surgery.

Analyzed studies typically included more males than females (the median study population was 57% male [range 36-83%]). Three-quarters of included studies included patients with a mean age of 70 years and above (range 59-77 years). Two studies reported a mean HTN duration of 13.5 years. [53, 79] See Appendix Table C.3.

The most common reason for angioplasty was HTN or renal insufficiency without prior treatment (42 studies).[15-17, 19, 21, 22, 28, 29, 34, 36-41, 44, 46, 48-50, 56-60, 62-65, 68-77, 79] Uncontrolled HTN while on two or more medications was another common indication for angioplasty (9 studies)[17, 34, 41, 56, 64, 71, 76, 77, 81].[45, 56, 62, 65, 69] Five studies included only patients with cardiovascular disease or flash pulmonary edema. [45, 56, 62, 65, 69] Across studies, the median average BP was 162/83 mmHg (range 110-196/73-105 mmHg); the median average GFR was 52 mL/min (range 31.5-67.2 mL/min), and median average SCr was 1.5 mg/dL (range 1.1-3 mg/dL) before PTRAS. See Appendix Table C.1.

Forty-five included studies reported on patients with a history or current cardiovascular disease. [14, 15, 17, 22, 24-26, 28, 33, 35, 37-41, 44-50, 53, 56, 58-60, 62-65, 67-73, 77-80] These 45 studies reported medians of 63 percent of patients who had coronary artery disease, 32 percent myocardial infarction, and 32 percent coronary revascularization. Medians of 22.5 percent of patients had CHF, and 29 percent left ventricular hypertrophy. Medians of 7 percent of patients had an abdominal aortic aneurysm, 39 percent cerebrovascular disease, and 16.5 percent a history of stroke. Lastly, a median of 44 percent of patients had a history of peripheral artery disease. See Appendix Table C.3.

The definitions of RAS varied across studies. Two studies included patients with over 80 percent stenosis,[17, 19] 23 over 70 percent stenosis,[14, 17, 21, 24, 26, 33, 35, 37, 38, 43, 45, 48, 51-53, 55, 57, 58, 62, 63, 65, 68-73, 77-79] 10 over 60 percent,[17, 22, 33, 38, 47, 67, 72, 77, 79, 81] and 21 over 50 percent. [15, 22, 24, 25, 34-38, 42, 44, 46, 50, 59-61, 64, 66, 70, 73, 77] The minimum percent stenosis was not stated in 9 studies.[16, 28, 29, 40, 41, 49, 54, 56, 71]

In 43 studies that reported data, bilateral stenting was present among a median of 28 (range 0-100%) percent of patients.[14-17, 21, 26, 33-38, 43-47, 49, 51-54, 56, 58, 62-72, 74-76, 78-80]

Palmaz stents were used in 25 studies,[14, 15, 33-36, 38-45, 47, 49-52, 55, 59, 70, 71, 73, 80] 20 studies (21 cohorts) used non-Palmaz stents or did not report stent brand information,[16, 17, 22, 31, 46, 48, 54, 58, 60, 62, 63, 65-68, 75, 77-79, 81] and 18 studies (19 cohorts) did not report data on the type of stent used.[19, 21, 24-26, 28, 29, 31, 37, 53, 56, 57, 61, 64, 69, 72, 74, 76] Twenty-five studies (26 cohorts) reported utilizing a distal protection device.[15-17, 22, 28, 34, 36, 40, 41, 46, 49, 50, 53-55, 59, 60, 62, 66-68, 77-80] See Appendix Tables C.2.1, C.2.3 C.2.4

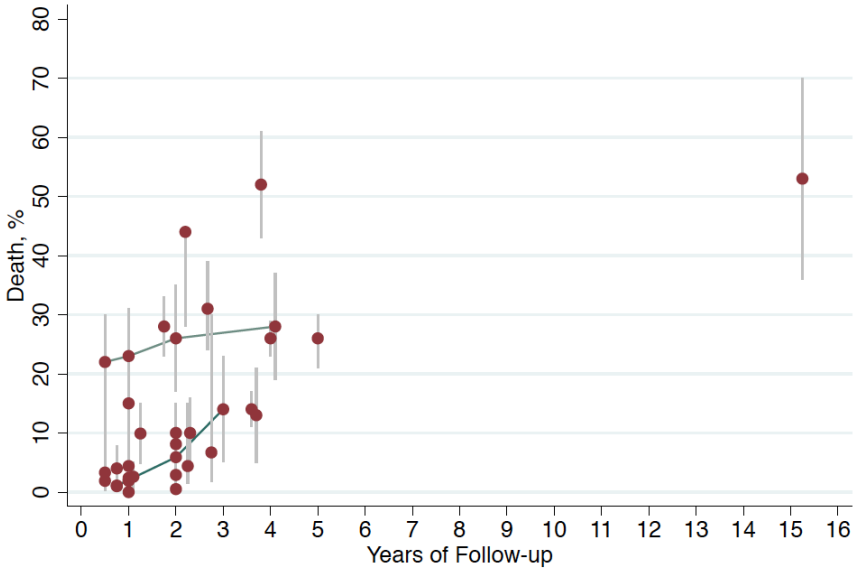
In general, across risk of bias questions, between 10 and 43 percent of studies were considered to be of high risk of bias, and between 57 and 90 percent were considered low risk of bias (Appendix Figure D.3). Twenty-five studies were judged high risk of bias for failing to adjust for different lengths of followup, 21 high risk of bias for incomplete outcome data

(attrition bias), and 14 for selective outcome reporting. The samples were considered to be representative of the entire population from which they were recruited in 48 studies.

Mortality (study duration 6 months or greater)

Data on mortality long-term mortality after PTRAS was reported in 31 studies (**Figure 7**).[15, 17, 25, 28, 31, 33-35, 37, 39-42, 44, 47-49, 56, 59, 62-68, 70, 74, 75, 78, 80] The mean followup time for reporting mortality was 2.4 years, with the longest followup at 15 years. The mortality rates ranged from 0 to 53 percent, with a median of 10 percent. Most studies reported mortality between 0 and 31 percent, but there are four included studies that reported mortality above 40 percent. These four studies reported that the intervention did not significantly reduce the risk of kidney failure and cardiac events. At 1 year, in about a third of the studies (10 of 31), 2.6 percent of patients had died (range 0% to 23%); at 2 years, in most studies (7 of 31), 8.1 percent of patients had died (range 0.5% to 44%). Other than a general trend toward increased death with longer-term followup, there was no clear explanation across studies for the difference in mortality. The most common cause of mortality reported was cardiovascular-related deaths (12 studies).[15, 17, 28, 36, 45, 46, 52, 56, 65, 66, 68, 72] Renal- and stroke-related deaths were reported in four[17, 28, 56, 66] and two[15, 17] studies, respectively. See Appendix Table C.4.1.

Figure 7. Death after PTRAS, percent of patients

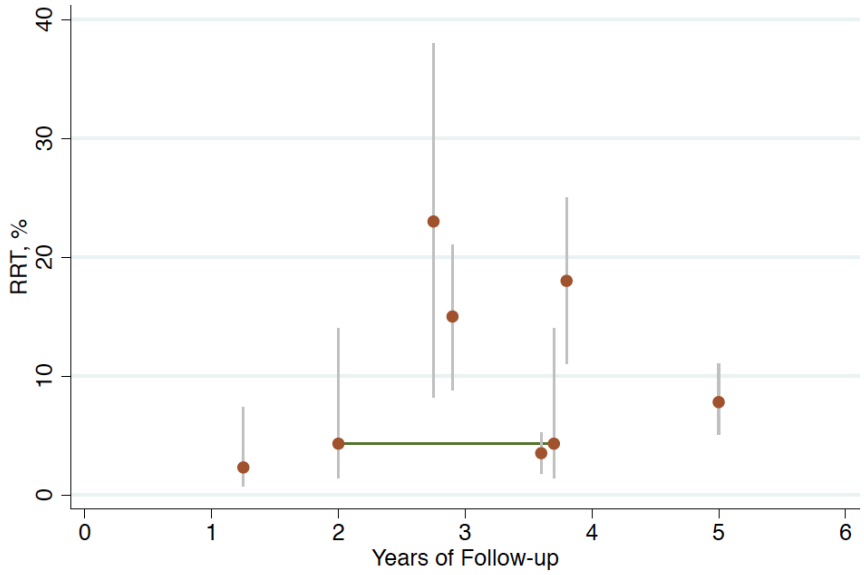


Point estimates and 95% confidence intervals from individual studies. Lines connecting points indicate data coming from the same study (or cohort) at different time points. Lines of the same thickness and color indicate data from different cohorts within the same study.

Renal replacement therapy

Seven studies[17, 25, 28, 40, 68, 74, 75] reported that RRT occurred in 2.3 to 23 percent of patients between 1.25 and 5 years (**Figure 8**). In three of the studies, RRT occurred in at least 15 percent of patients. Additionally, three studies reported RRT occurred in less than 5 percent of patients. There was no clear explanation across studies for the wide heterogeneity in RRT occurrence, including length of followup. See Appendix Table C.4.6.

Figure 8. Renal replacement therapy after PTRAS, percent of patients



Point estimates and 95% confidence intervals from individual studies. Lines connecting points indicate data coming from the same study (or cohort) at different time points. Lines of the same thickness and color indicate data from different cohorts within the same study. RRT = renal replacement therapy.

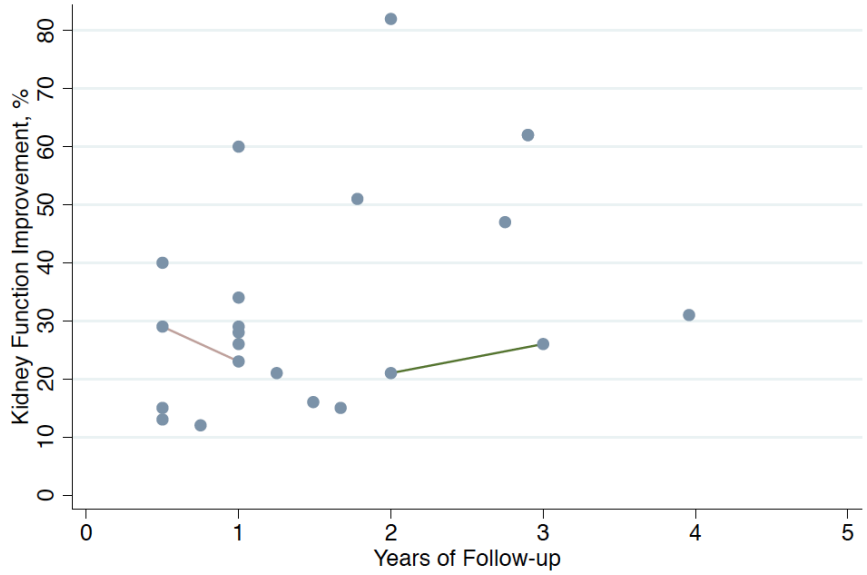
Cardiovascular outcomes

Twelve studies[15, 17, 25, 28, 31, 40, 47, 57, 59, 68, 70, 72] reported cardiovascular event rates, indicating that patients remain at increased risk of cardiovascular disease after PTRAS. CHF was reported in four studies (0 to 83%). Other cardiovascular events included angina in 7.5 percent (one study)[28], MI in 1 to 82 percent (eight studies)[17, 28, 40, 47, 59, 68, 70, 72], stroke in 1.2 to 19 percent (six studies),[17, 28, 31, 47, 68, 72] coronary revascularization in 3.8 to 3.9 percent (two studies),[28, 40] and composite cardiovascular events in 0 to 37 percent (four studies).[25, 28, 57, 72] See Appendix Tables C.4.16 and C.4.17.

Kidney function

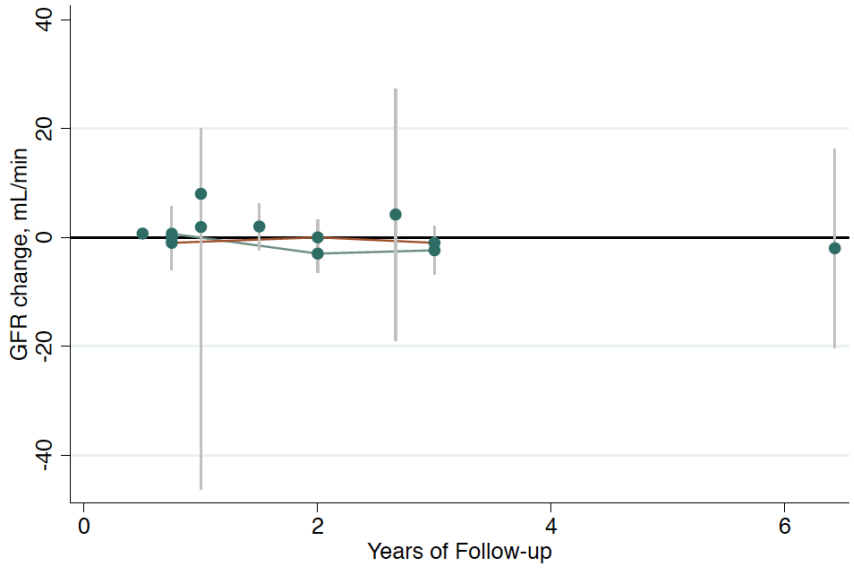
Four studies[28, 72, 78, 80] reported that between 1.9 and 82 percent of patients had episodes of acute kidney injury at 1 to 3 years. Twenty-two studies reported ordinal outcomes for kidney function improvement (**Figure 9**).[17, 22, 28, 35, 38, 40, 45, 46, 50, 52-54, 57, 59, 63, 66, 67, 74-76, 78, 80] Kidney function improved in 12 to 82 percent of patients (14 studies),[22, 28, 38, 40, 46, 53, 54, 57, 63, 66, 75, 78, 80]; did not change in 3.2 to 72 percent (11 studies),[22, 28, 38, 40, 46, 53, 54, 63, 75, 80] stabilized in 33 to 59 percent (two studies),[54, 66] and worsened in 3.8 to 37 percent (15 studies).[22, 28, 32, 38, 40, 46, 50, 53, 57, 63, 66, 75, 78, 80] Twenty-one studies reported a median 0 mL/min change in GFR (range -9 to 10 mL/mL) (**Figure 10**).[22, 24, 28, 43, 52, 53, 55, 56, 61-63, 66, 68, 70, 72, 74, 77-79, 81] Twenty-seven studies reported a median −0.1 mg/dL change in SCr (range −0.8 to 1.7 mg/dL).[16, 28, 34, 37-39, 41, 43, 44, 46, 49, 50, 53-57, 59, 61-64, 68, 69, 73, 76, 78] There was no clear explanation across studies for the wide heterogeneity in change in kidney function. For details, see Appendix Tables C.4.2, C.4.6, and C.4.7.

Figure 9. Kidney function improvement after PTRAS, percent of patients



Point estimates and 95% confidence intervals from individual studies. Lines connecting points indicate data coming from the same study (or cohort) at different time points. Lines of the same thickness and color indicate data from different cohorts within the same study.

Figure 10. GFR change (in mL/min) after PTRAS



Point estimates and 95% confidence intervals from individual studies. Lines connecting points indicate data coming from the same study (or cohort) at different time points. Lines of the same thickness and color indicate data from different cohorts within the same study.

Blood pressure control

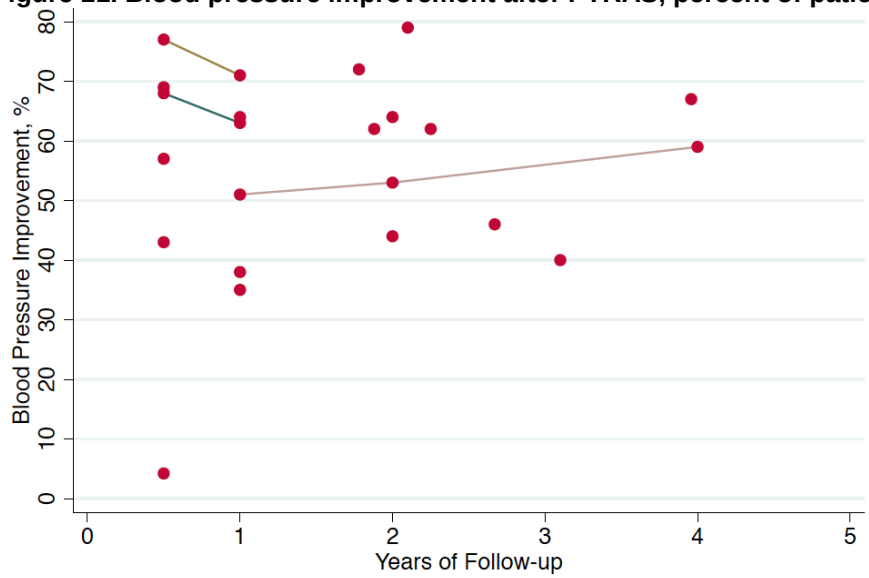
New-onset HTN was reported in 0 to 3.9 percent (two studies).[15, 47] Ordinal outcomes for BP improvement were reported in 19 studies (**Figure 11**). In these studies, BP improved in 4.2 to 69 percent (15 studies),[33, 34, 37, 38, 50, 57, 59, 63, 64, 66, 67, 69, 72] did not change in 9.1 to 54 percent (10 studies),[33, 34, 37, 57, 59, 63, 69, 72] and stabilized or worsened in 7.4 to 67 percent (5 studies).[32, 33, 38, 50, 72]

Changes in BP were reported in 36 studies[16, 17, 22, 24, 28, 33, 34, 36-39, 41-44, 48-50, 52, 53, 55-57, 59, 62-64, 66, 69, 70, 72, 73, 77-79, 81] (**Figure 12**); 33 studies reported a -17 mmHg median change in SBP (range -51 to 28 mmHg),[17, 22, 24, 28, 33, 36-38, 41-44, 49, 50, 52, 53, 55-57, 59, 62-64, 66, 68-70, 72, 73, 77-79, 81] 31 studies reported a -6 mmHg median change in DBP (range -30 to 5 mmHg),[22, 24, 28, 33, 36-38, 41-44, 49, 50, 52, 53, 55-57, 59, 62-64, 66, 69, 70, 72, 73, 77-79, 81] and five studies reported a -13.7 mmHg median change in MAP (range -29 to 6 mmHg).[34, 37, 39, 48, 70] See Appendix Tables C.4.8, C.4.10, and C.4.11.

Changes in number of antihypertensive medications were reported in 30 studies **(Figure 13)**.[17, 33, 35, 36, 38-42, 45-49, 52, 53, 55-57, 59, 63, 64, 67-72, 78, 79] These studies reported a median -0.3 change in the number of antihypertensive medications (1.4 decrease to 1.2 increase). For details, see Appendix Tables C.4.8, C.4.12, and C.4.13.

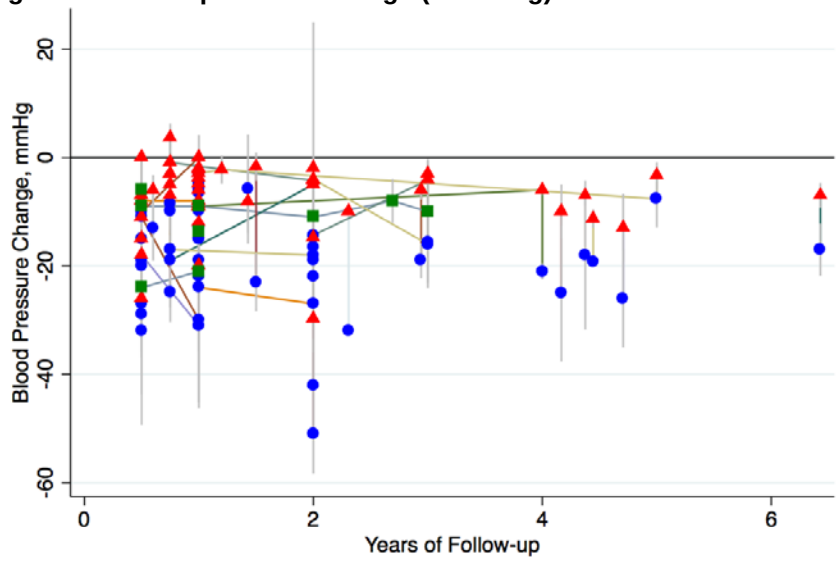
For all blood pressure outcomes, there were no clear explanations for the wide heterogeneity across studies in outcomes after stent.

Figure 11. Blood pressure improvement after PTRAS, percent of patients



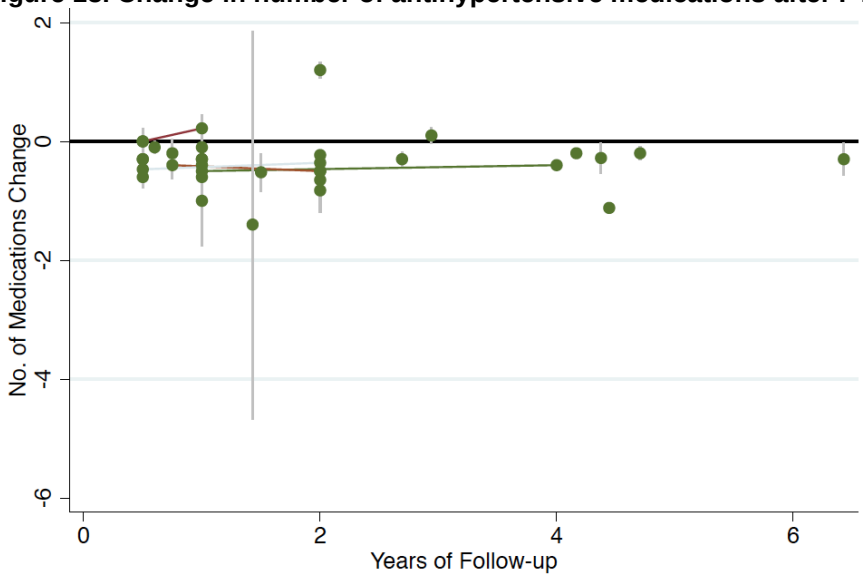
Point estimates and 95% confidence intervals from individual studies. Lines connecting points indicate data coming from the same study (or cohort) at different time points. Lines of the same thickness and color indicate data from different cohorts within the same study.

Figure 12. Blood pressure change (in mmHg) after PTRAS



Point estimates and 95% confidence intervals from individual studies. Blue circles = systolic blood pressure; red triangles = diastolic blood pressure; green squares = mean arterial pressure. Lines connecting points indicate data coming from the same study (or cohort) at different time points. Lines of the same thickness and color indicate data from different cohorts within the same study.

Figure 13. Change in number of antihypertensive medications after PTRAS



Point estimates and 95% confidence intervals from individual studies. Lines connecting points indicate data coming from the same study (or cohort) at different time points. Lines of the same thickness and color indicate data from different cohorts within the same study.

Adverse events (including 30-day mortality)

A total of 19 studies reported adverse events immediately following PTRAS.[28, 34-38, 40, 43, 44, 46, 50, 51, 53, 54, 59, 64, 67, 68, 72] The 30-day mortality was reported in 9 studies and ranged from 0 to 15 percent.[31, 33, 37, 42, 63-65, 78, 80] Other reported adverse events included RRT 1.5 to 3.1 percent (two studies),[40, 74] acute renal failure 2.3 to 11 percent (two studies),[28, 67] severe bleeding 1.6 to 31 percent (nine studies),[33, 35, 43, 51, 56, 60, 64, 67, 72] dissection 2.2 to 3.9 percent (two studies),[57, 67]

unplanned surgery 0 to 6 percent (one study),[40] and thrombosis 0 to 12 percent (three studies).[28, 38, 67] See Appendix Tables C.4.18 and C.4.19.

Key Question 2. Association of patient factors with outcomes

Twenty studies of PTRAS[13, 18, 23, 39, 42, 43, 47, 48, 52-54, 64, 66-68, 70, 72, 74-76] reported analyses of patient-level (or disease characteristic) factors associated with outcomes of interest (**Tables 1 and 2**).

Three studies evaluated subgroups of patients as predictors of requiring RRT (**Table 1**). Kane 2010 found that patients with CHF were significantly more likely to develop RRT (RR 2.3; 95% CI 1.1, 5.0), adjusted for sex, age, and SCr.[23] Both Mannarino 2012 and Valluri 2012 found no difference between patients with bilateral or unilateral stenosis.[74, 75] Valluri 2012 also found no difference between those patients with relatively rapid kidney function decline prior to PTRAS compared to other patients.[74]

Eleven studies evaluated a variety of potential predictors for long-term kidney function (**Table 1**). Six of eight studies found that patients with *worse* pre-PTRAS kidney function were more likely to have improved kidney function after PTRAS than other patients; the other two found no significant association. Three studies each found that patients with bilateral stenosis either had greater improvement than those with unilateral stenosis or there was no significant association. No other factors potentially predicting kidney function were evaluated by more than three studies.

Eight studies evaluated predictors of long-term BP outcomes (**Table 1**). Three of five studies found that patients with higher pre-PTRAS BP were more likely to have BP improvement than other patients; the other two studies found no association. Four found no association between pre-PTRAS kidney function and BP, but two found that patients with worse kidney function (GFR <40 or 50 mL/min) were significantly less likely to have BP improvement. Only one of four studies found that patients with bilateral disease were more likely to have BP improvement; the other three found no association. No other factors potentially predicting kidney function were evaluated by more than three studies.

Five studies evaluated predictors of all-cause death (**Table 2**). Three of four studies found that patients with worse pre-PTRAS kidney function were significantly more likely to die; the fourth found no association. Three found no association with a history of coronary artery disease, but one of these did find that significantly more patients who had had a myocardial infarction died. This study also found that patients with bilateral stenosis were more likely to die, but two other studies found no association.

Three studies evaluated composite outcomes that included all-cause or cardiovascular death, various cardiovascular events, and in some instances RRT, acute kidney injury, CHF, uncontrolled HTN, or revascularization (**Table 2**). All three tested histories of various cardiovascular diseases. Rzeznik 2011 found that coronary artery disease severity (which was not defined) increased the risk of the composite outcome. However, Kennedy 2003 and Trani 2010 found that coronary artery disease, myocardial infarction, and peripheral vascular disease were not associated with outcomes. All four also evaluated pre-PTRAS left ventricular function; two studies found increase risk of outcomes with a history of CHF, but two found no associations with left ventricular mass or ejection fraction.

Key Question 3.
Association of treatment factors with outcomes

In a subgroup analysis of a retrospective study, Beck 2010 found that neither use of gold-coated stents or embolic protection were associated with BP at 1.5 years.[67]

In an observational comparative study, Zahringer 2007 found no differences at 2 years in BP, HTN cure, the number of antihypertensive medications, SCr, or kidney function worsening between patients who had angioplasty with either sirolimus eluting or bare stents.[59]

In a RCT, Lekston 2008 found no difference in 10 month SCr between those who received or did not receive intraluminal brachytherapy during stenting.[61]

Table 1. Independent predictors of kidney and blood pressure outcomes after angioplasty with stent

Outcome Study	**Mean F/up (*Metric*)**	**CKD**	**Pre-Stent ΔGFR**	**Bilat**	**Stenosis Grade**	**CAD**	**Sex**	**BP**	**Age**	**Misc**	**Other NS**
RRT											
Kane 2010**	5 y (***RR***)									CHF: 2.3 (1.1, 5.0)	
Mannarino 2012	2.75 y (***%***)			NS*							
Valluri 2012	2.9 y (***%***)		Fast vs. Slow: NS*	NS*							
Kidney Function											
Arthurs 2007	1.25 y (***SCr slope***)	SCr ≥1.5: −0.03/mo SCr <1.5: 0.03/mo P<0.05		NS*							RI >0.8
Holden 2006	1.3 y (*Imp*)	Stage NS*									
Leesar 2009	1 y (*SCr*)										HSG*
Mannarino 2012	2.75 y (***GFR/mo***)		Fast: 0.01 Slow: −0.14 P=0.04*	Bilat: 0.02 Unilat: −0.16 P=0.02							Proteinuria
	2.75 y (*GFR imp, **OR***)		16 (1.5, 166)	NS							
Ramos 2003	1 y (***GFR***)	GFR<50: 20.7 GFR≥50: −4.8 P sig, implied*									
Rivolta 2005	1.67 y (***1/SCr slope***)	SCr NS									Kidney diameter
Sapoval 2010	1 y (*GFR imp, **%***)	CKD 1/2: 3.5% CKD 3: 23% CKD 4: 50% P nd*									

Outcome Study	**Mean F/up (*Metric*)**	**CKD**	**Pre-Stent ΔGFR**	**Bilat**	**Stenosis Grade**	**CAD**	**Sex**	**BP**	**Age**	**Misc**	**Other NS**
	1 y (***GFR***)	CKD 1/2: −25 CKD 3: 1 CKD 4: 13 CKD 5: 24 P nd*									
Trani 2013	6 mo (*SCr imp, **OR***)	SCr, per quartile 2.5 (1.3, 4.7)		NS	NS†		NS*		NS	CRP per quartile 0.39 (0.19, 0.82)	LVEF, Statins, ACEi/ARB, DM
Tsao 2005	6 mo (***GFR***)	NS*		Bilat: 5 Unilat: −10 P<0.001							
	6 mo (*SCr imp, **%***)	SCr >1.5: 24% SCr ≤1.5: 0% P nd*			NS (≥90%)						HTN duration
Valluri 2012	2.9 y (*GFR slope imp*)			NS*			NS*				
Zeller 2004	2.67 y (***SCr***)	SCr (>3.0 vs. <1.2 mg/dL): −0.9 (−1.3, −0.6) P<0.001 SCr (1.21-3.0 vs <1.2 mg/dL): −0.2 (−0.3, 0) P<0.009*′‡		NS*′‡							RI*′‡, DM*′‡
	2.67 y (*SCr imp, **OR***)	SCr† 2.57 (1.55, 4.25)		2.04 (1.01, 4.21)	1.05 (1.04, 1.09)†	3v: 0.39 (0.17, 0.91)					
Blood Pressure											
Beck 2010	1.5 y (*no imp, **OR***)	GFR<40: 1.6 (1.0, 2.9)		NS		NS	F: 1.3 (1.0, 2.1)	SBP>180 NS DBP>90 NS	>70 NS		AAA, DM, COPD, Dyslipidemia, Smoking
Leesar 2009	1 y (*imp, **OR***)							NS		HSG ≥21 mmHg: 1.32 (1.05, 1.65)	Other renal artery measures§
Ramos 2003	1 y (***mmHg***)	GFR<50: −10/−4 GFR ≥50: −21/−10 P nd*									

Outcome Study	**Mean F/up (*Metric*)**	**CKD**	**Pre-Stent ΔGFR**	**Bilat**	**Stenosis Grade**	**CAD**	**Sex**	**BP**	**Age**	**Misc**	**Other NS**
Rocha-Singh 1999	13 mo (*response*[#], ***OR***)	SCr>1.4 NS		4.6, P=0.009		NS	NS	MAP >110: 2.9, P=0.003	NS		DM, Ostial lesion, Solitary kidney
Rzeznik 2011	1 y (*imp,* ***RR***)	NS		NS	1.28 (1.08, 1.51)†	NS		DBP: 1.74 (1.47, 2.06)† SBP NS			Echocardiography measures
Staub 2010	6 mo (*imp,* ***OR***)	NS					NS	MAP per mmHg 1.05 (1.01, 1.20)	Per y, 0.95 (0.89, 0.99)	BNP >50 4.0 (1.2, 13.2)	RI
Tsao 2005	6 mo (***mmHg***)	NS									
Zeller 2004	2.67 y (*imp,* ***OR***)			NS						No. Rx† 1.81 (1.38, 2.36)	DM, RI
BP or SCr¶											
Gill-Leertouwer, 2002	1 y (*imp,* ***OR***)	GFR per mL/min 0.92 (0.85, 0.998)			NS						Other renal artery measures||
No. Rx											
Leesar 2009	1 y (***mean number***)									HSG ≥21: 2.3 HSG <21: 3.4 P<0.01*	
Tsao 2005	6 mo (***mean number***)	NS*									

* Univariate

† Categorization not defined; implied that higher grade associated with improvement.

‡ Estimated based on reported data.

§ Intravascular ultrasound measures (mean lumen area, area stenosis, minimum lumen diameter, plaque plus media area), pressure guidewire measures (fractional flow reserve, hyperemic mean gradient, resting systolic gradient, renal angiography measures (minimum lumen diameter, diameter stenosis).

DBP ≤90 mmHg with no change in medications or or decrease in ≥1 medications; or DBP 90-100 mmHg and decrease in MAP ≥5 mmHg and no change in medications.

¶ DBP decrease ≥10 mmHg or SCr decrease ≥20% depending on indication

|| Intravascular ultrasound measures, renal scintigraphy measure.

** Kane 2010 was a retrospective comparative study of angioplasty with stent to medical therapy.[23] Therefore, this studies did not meet eligibility criteria for Key Question 1 for PTRAS cohorts and was not included there.

3v = 3 vessel coronary artery disease, AAA = abdominal aortic aneurysm, ACEi/ARB = angiotensin converting enzyme inhibitor or angiotensin receptor blockers, Aortic Dz = Severe aortic occlusive disease, Bilat = bilateral stenosis, BNP = brain natriuretic protein (in pg/mL), CAD = coronary artery disease, CHF = congestive heart failure, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CorRevasc = coronary revascularization, CRP = C reactive protein, DBP = diastolic blood pressure, DBP = diastolic blood pressure (in mmHg), DDx = diastolic dysfunction moderate or severe (vs. mild or none), DM = diabetes mellitus, DM = diabetes mellitus, F = female, F/up = followup, Fast =

fast progressor (more than −0.25 mL/mo preprocedure), GFR = glomerular filtration rate (in mL/min), GFR = glomerular filtration rate (unit used in regression not reported), HR = hazard ratio, HSG = Pressure guidewire-measured hyperemic systolic gradient, imp = improvement, imp = improvement, LVEF = left ventricular ejection fraction, MAP = mean arterial pressure, MI = myocardial infarction, Misc = miscellaneous, nd = no data, No. Rx = number of antihypertensive medications, Other NS = nonsignificant predictors not otherwise listed, RI = resistance index, RR = risk ratio, Rx = number of antihypertensive medications, SBP = systolic blood pressure (in mmHg), SBP = systolic blood pressure (unit used in regression not reported), SCr = serum creatinine (in mg/dL), sig = significant, Slow = slow progressor (less than −0.25 mL/mo preprocedure), Unilat = unilateral stenosis, ΔGFR = rapid kidney function decline (>80th percentile preprocedure) or fast progressor (more than −0.25 mL/mo preprocedure).

Table 2. Independent predictors of clinical event outcomes after angioplasty with stent

Outcome Study	Mean F/up (*Metric*)	CKD	BP	Bilat	CVD	CHF	Age	DM	Smoking	Misc	Other NS
Death											
Crutchley 2009*	4.8 y (***HR***)									RI>0.8: 6.7† (2.6, 17)	
Kane 2010**	5 y (***RR***)	SCr, per mg/dL: 2.7 (1.1, 6.6)			CAD NS	3.4 (2.0, 5.7)		NS			HTN
Kennedy 2003	1.75 y (***%***)	SCr (higher) P=0.001		32% v 25% P<0.01	MI 36% v 24% P<0.05‡ CAD NS	56% v 15% P<0.001‡		NS	NS		Sex, Race
Mannarino 2012	2.75 y (***%***)			NS‡							
Valluri 2012	2.9 y (***%***)	Rapid decline NS‡		NS‡							
Death, CV or Renal											
Kennedy 2003	1.75 y (***%***)	SCr (higher) P=0.001			CAD NS						
Composite											
CV death, RRT or SCr increase >30%, MI, Stroke, CHF, Uncontrolled HTN											
Kennedy 2003	1.75 y (***%***)			48% v 30% P<0.01‡	CAD NS‡ MI NS‡	53% v 30% P<0.01‡		51% v 31% P<0.01‡	NS		Sex, Race
CV death, MI, Stroke, Revascularization											
Rzeznik 2011	1 y (***RR***)	GFR NS		NS	CAD severity§ 1.27 (1.04, 1.56)	LVM NS			1.29 (1.05, 1.57)		BP, Stenosis grade
CV death, RRT, MI, Stroke											
Trani 2010	2 y (***OR***)	SCr per mg/dL 2.20 (1.11, 4.38)		7.32 (1.53, 35.1)	PVD NS	LVEF NS	NS	NS			Sex, Stenosis grade
Myocardial Infarction											
Kennedy 2003	1.75 y (***%***)	SCr (higher) P=0.001			CAD NS						
Congestive Heart Failure											
Kennedy 2003	1.75 y (***%***)	SCr (higher) P=0.001			CAD NS						

* Crutchley 2004 was a retrospective comparative study of surgery vs. angioplasty with stent with <100 participants in the surgical arm.[18] Therefore, this studies did not meet eligibility criteria for Key Question 1 for surgical cohorts and was not included there.

† HR for combined surgery and angioplasty with stent groups, described in text and graphically as similar results for both intervention groups.
‡ Univariate analysis.
§ Categorization not defined
** Kane 2010 was a retrospective comparative study of angioplasty with stent to medical therapy.[23] Therefore, this studies did not meet eligibility criteria for Key Question 1 for PTRAS cohorts and was not included there.

Bilat = bilateral stenosis, BP = blood pressure, CAD = coronary artery disease, CAD = coronary artery disease, CHF = congestive heart failure, CKD = chronic kidney disease, CV = cardiovascular, CVD = cardiovascular diseases, DM = diabetes mellitus, F/up = followup, GFR = glomerular filtration rate (in mL/min), HR = hazard ratio, HTN = hypertension, LVEF = left ventricular ejection fraction, LVM = left ventricle mass, MI = myocardial infarction, Misc = miscellaneous, NS = nonsignificant, OR = odds ratio, Other NS = nonsignificant predictors not otherwise listed, PVD = peripheral vascular disease, RI = resistance index, RR = risk ratio, RRT = renal replacement therapy, SCr = serum creatinine (in mg/dL).

Medical therapy only

Key points

- 20 cohorts of patients (in 17 prospective studies) reported outcomes in patients receiving medical therapy alone. The studies were highly heterogeneous in both their included patients and specific medical treatments (both within and across studies). Many of the studies were deemed to be at high risk of bias for failure to adjust for different lengths of followup and attrition bias.
- **Mortality**: In 10 studies, mortality ranged from 9 to 56 percent after 2 to 9 years of followup. Other than a general trend toward increased death with longer-term followup, there was no clear explanation across studies for the difference in mortality.
- **RRT**: In 7 studies, incident RRT occurred in 2 to 18 percent of patients between 3 and 5 years, but with no clear explanation of the heterogeneity across studies, including length of followup.
- **Cardiovascular outcomes**: In 9 studies, various cardiovascular outcomes were reported to occur, but with highly heterogeneous percentages of patients (including CHF 1.4-13%, MI 2.5-83%, stroke 2.5-23%).
- **Kidney function**: 10 studies reported on kidney function outcomes. Kidney function improvement occurred in 0 to 26 percent of patients and deteriorated in 19 to 38 percent of patients (4 studies). In 3 studies, GFR changed by −0.7 to 8 mL/min between 1 and 6 years of followup and SCr changed by −0.1 and 1.3 mg/dL at between 1 and 5 years of followup In 4 studies 2 to 82 percent of patients had episodes of acute kidney injury. In 21 studies, kidney function improved in 12 to 82 percent and worsened in 4 to 37 percent of patients. 21 studies had a median change in GFR of 0 mL/min (range -9 to 10 mL/mL). There was no clear explanation across studies for the wide heterogeneity in change in kidney function.
- **BP control**: 12 studies reported on BP outcomes. In 1 study 4 percent of patients became newly hypertensive and none had a hypertensive crisis. In 10 studies, systolic BP changed by -6 to -22 mmHg and diastolic BP by -1 to -13 mmHg. In 2 studies, the number of antihypertensive medications was unchanged after 1.75 years of followup and increased by 1.4 medications after 3.6 years.
- **ACEi/ARB use**: 2 studies found increases in the percentage of patients on ACEi or ARB after 1 year from 79 to 83 percent 1 year in one study and from 38 to 43 percent in the other.
- **Adverse events**: No study reported on adverse events related to medication use.
- **Patient factors**: 2 studies reported on patient-level predictors of clinical outcomes. In one study each, statistically significant associations were found between flash pulmonary edema and both death and cardiovascular events, between lower GFR and RRT, and a near significant association between proteinuria and RRT. No associations were found between flash pulmonary edema and RRT, lower GFR and death, or between rapid kidney function deterioration, refractory HTN, sex, or history of coronary artery disease and clinical outcomes.
- **Treatment factors**: 2 studies addressed differences in treatment factors as predictors of outcomes. One study found no association between beta blockers or angiotensin inhibitors and death or RRT, but the second study found that angiotensin inhibitor use was associated

with reduced cardiovascular events and statin use was associated with reduced cardiorenal events, death and RRT.

Key Question 1.
Effects of intervention on outcomes

In 17 articles, [15-17, 21, 22, 24-26, 28, 29, 42, 82-88] we identified 20 cohorts of patients who were treated with medical therapy only (a total of 7778 patients) in prospective studies. Among the studies, nine cohorts assessed the effectiveness of medical therapy on outcomes in single cohorts of patients (or compared different cohorts of patients receiving medical therapy) and 12 cohorts were from studies comparing medical therapy to PTRAS; one study provided analyses relevant only to Key Question 3.[86, 87]

Only Hackam 2011 explicitly reported consecutive enrollment of patients.[87] Four studies reported the presence of HTN as an additional inclusion criterion.[16, 17, 83, 85] One study required that patients be over 65 years of age.[87] One study specifically included patients with chronic kidney disease.[17] The studies mostly included men, with a median average of 64 percent male (range 43-96%). The median average age across the studies was 69.5 years old (range 60.9-78 years). The percentage of patients with bilateral ARAS ranged from 18 to 55 percent. The median average baseline BP across studies was 154/79 mmHg (range 131-175.4/74-95 mmHG). The median average baseline GFR was 40 mL/min (range 33-66.2 mL/min), and SCr was 1.8 mg/dL (range 1-2.29 mg/dL).

The definitions of ARAS varied across studies. Six studies included patients with over 50 percent stenosis[15, 24, 25, 82, 83, 85] (one of which required that patients had less than 80% stenosis [24]), one with over 60 percent stenosis,[88] three with over 70 percent or 75 percent stenosis,[21, 26, 27] and two with over 80 percent stenosis.[17, 84] The percent stenosis was not reported in four studies. One study was multicenter and had different definitions at the two centers. [22] See Appendix Table C.1 for eligibility criteria and Table C.2.2 for arm details.

None of the studies reported on the patients' history of coronary artery revascularization or concomitant aortic disease; however, one study reported that 26.5 percent of patients had concomitant cerebrovascular disease.[22] In four studies, between 36 and 60 percent of patients had concomitant peripheral vascular disease,[25, 26, 28, 84] and in two studies 19 and 40 percent of patients had a history of stroke.[26, 28] One study reported that 36 percent of patients had peripheral artery disease,[83] and another reported 50 percent of patients had carotid stenosis.[26] See Appendix Table C.3 for full baseline data.

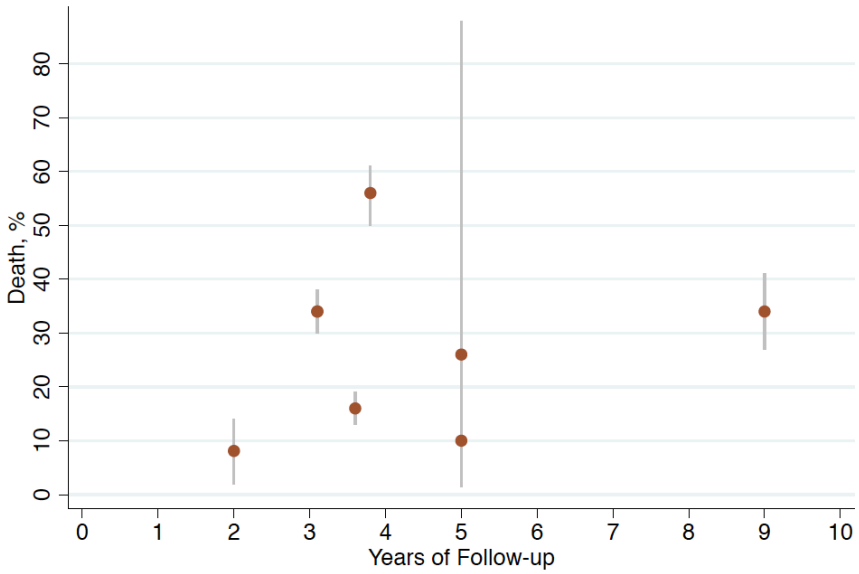
Among the 17 studies, only three are newly published since the 2006 and 2007 reports. The risk of bias for all studies is summarized in Appendix Figure D.4. About half the studies were of high risk of bias for adjusting for different lengths of patient followup and for incomplete outcome data (attrition bias). All studies were of low risk of bias for sample representing the entire population. About half the studies were deemed to be at low risk of selective reporting bias and the other half unclear risk of bias.

Mortality (study duration 6 months or greater)

Data on long-term mortality was reported in ten studies (**Figure 14**). All-cause death was reported in 9 to 56 percent of patients (seven studies)[15, 17, 25, 26, 28, 83, 88] followed for 2 to 9 years; higher death rates were generally found in longer followup studies. Death as a result of stroke occurred in 5.4 to 85 percent of patients (two studies)[15, 17] followed for 2 to 5 years,

cardiovascular related deaths occurred in 5.4 to 16 percent of patients (four studies)[15, 17, 26, 84] followed for 2 to 7 years, and renal related deaths occurred in 4.2 percent of patients (one study)[28] followed for 5 years. For details, see Appendix Table C.4.1.

Figure 14. Death while on medical therapy, percent of patients

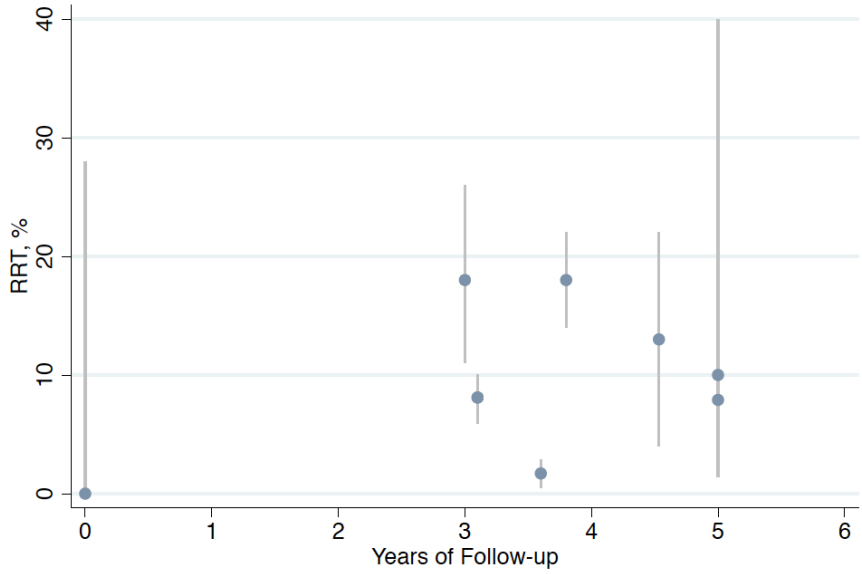


Point estimates and 95% confidence intervals from individual studies.

Renal replacement therapy

Among seven studies that reported 3 to 5 year followup, between 2 and 18 percent of patients required RRT, with a median of 10 percent (**Figure 15**).[17, 25, 26, 28, 82, 84, 85] There is no clear explanation for the wide range of rates of RRT. See Appendix Table C.4.6.

Figure 15. Renal replacement therapy while on medical therapy, percent of patients



Point estimates and 95% confidence intervals from individual studies.

Cardiovascular outcomes

Overall, nine studies reported on cardiovascular outcomes. Three studies reported data on CHF events.[15,26,28] Followup times ranged from 3 months to 7.4 years, and incidence ranged from 1.4 to 13 percent. One study reported a 1.4 percent incidence of flash pulmonary edema at 2-year followup.[15] A second study reported a 10 percent incidence of abdominal aortic aneurysm rupture at 7.4-year followup.[26] The third study reported an incidence of 8.6 percent of angina resulting in hospitalization at 5-year followup.[28] This latter study reported that 4.1 percent of patients followed for 5 years required a coronary artery procedure.[28]

Four studies reported on incidence of MI, one of which reported that no patients experienced MI during followup.[26] Incidence in the other three studies ranged from 2.5 to 83 percent in patients who were observed from 1.75 to 5 years.[17, 21, 28] Data on incidence of stroke was reported in 5 studies, one of which reported that no patients had a stroke during followup.[13] Incidence of stroke in the other four studies ranged from 2.5 to 23 percent in patients who were observed from 1.75 to 5 years.[17, 21, 28, 85]

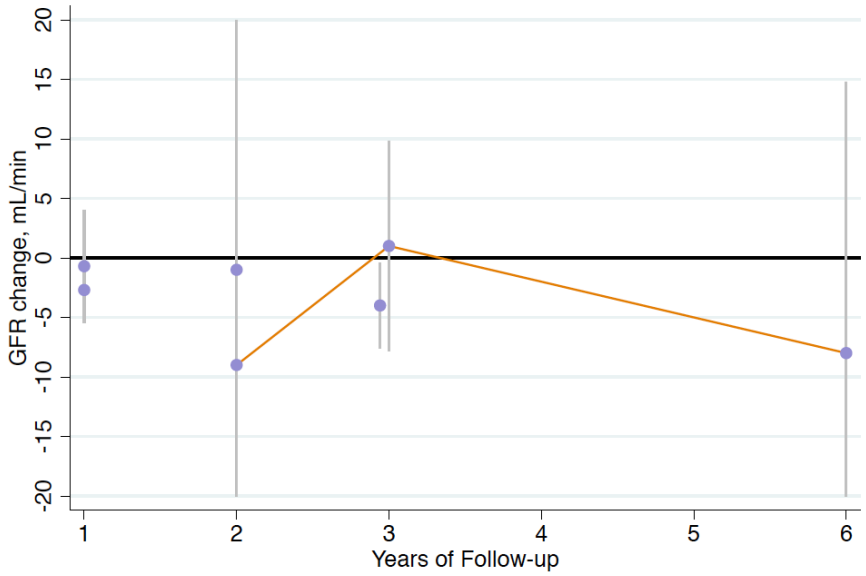
One study reported that 12 percent of patients had a new cardiovascular event (new onset angina, ischemic heart disease, myocardial infarction, revascularization, CHF hospitalization, peripheral vascular disease, or stroke or TIA) at a median of 3.1 years.[88] In addition, 42 percent had a composite outcome that also included death and RRT. Another study reported that 57 percent had a composite cardiorenal outcome that included death, cardiovascular event (myocardial infarction, stroke, CHF), and RRT or acute kidney injury at a mean of 3.3 years.[87] See Appendix Tables C.4.16 and C.4.17.

Kidney function

Overall, 10 studies reported on kidney function outcomes. Three studies reported data on improvement of kidney function. In two of the studies, improvements occurred in 19 and 26 percent of patients who were observed for 1 year;[22, 28] in one study no patients improved at 4-year followup.[29] The studies reported no change in kidney function in 35 to 65 percent of patients. A fourth study only reported on the percentage of patients whose kidney function deteriorated.[17] Across the four studies, 19 to 38 percent of patients experienced deterioration in kidney function. In one study, at 5-year followup, 5.9 percent of patients had experienced acute kidney injury.[28]

Three studies reported a decrease of between 0.7 and 8 mL/min in GFR at between 1 and 6 years of followup (**Figure 16**).[22, 24, 26, 84] One study reported an average decrease in 1/SCr of 0.012 dL/mg per year over 5 years.[28] Four studies reported a change in SCr of between −0.1 and 1.3 mg/dL at between 1 and 5 years of followup.[16, 21, 28, 82] For details, see Appendix Tables C.4.3, C.4.6, and C.4.7.

Figure 16. GFR change (in mL/min) while on medical therapy



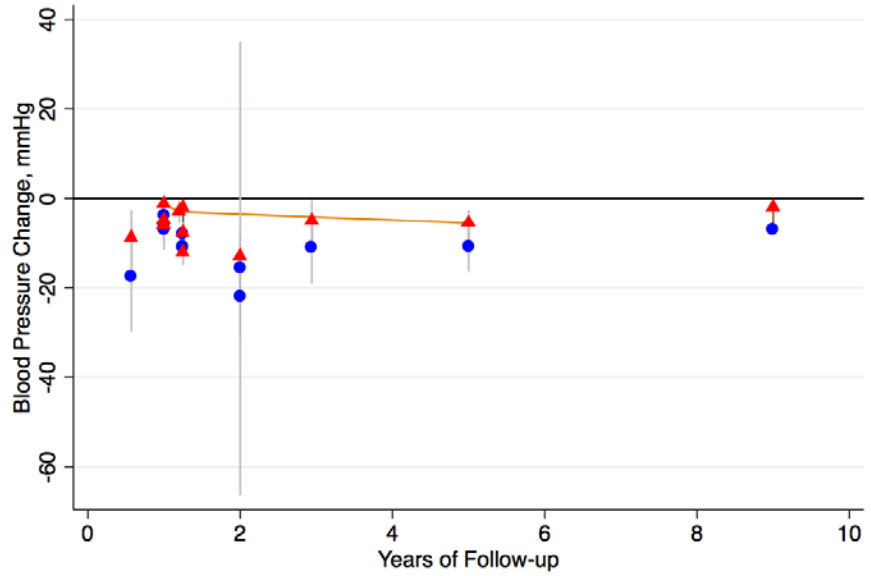
Point estimates and 95% confidence intervals from individual studies. The line connecting points indicate data coming from the same study (or cohort) at different time points.

Blood pressure control

Only one study reported data on incidence of HTN and hypertensive crises.[15] At 2-year followup, 4.1 percent of patients became newly hypertensive, while none experienced a hypertensive crisis.[15] Data on change in SBP was reported in 10 studies (**Figure 17**), which found decreases in SBP between 6 and 22 mmHg in patients who were observed from 1 to 9 years. [16, 17, 21, 22, 24, 26, 28, 82-85] Nine studies reported data on change in DBP, with decreases ranging from 1 to 13 mmHg in patients who were observed from 1 to 9 years. [21, 22, 24, 26, 28, 82-85]

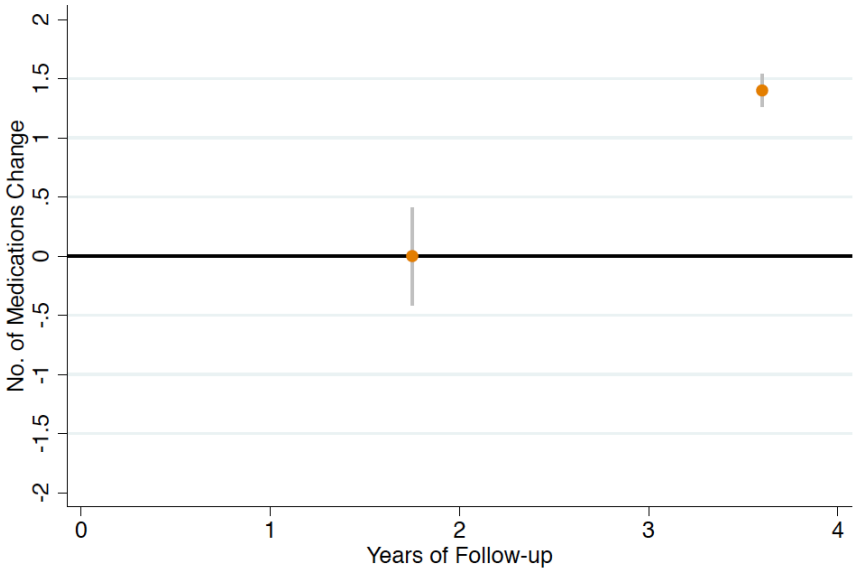
Two studies reported data on the change in number of antihypertensive medications from baseline to maximum followup (**Figure 18**). One study reported no change in the average number of medications at 1.75-year followup,[21] while the other reported an increase of 1.4 medications for patients who were observed for 3.6 years.[17] For details, see Appendix Tables C.4.9, C.4.12, and C.4.13.

Figure 17. Blood pressure change (in mmHg) while on medical therapy



Point estimates and 95% confidence intervals from individual studies. Blue circles = systolic blood pressure; red triangles = diastolic blood pressure; green squares = mean arterial pressure. The line connecting points indicate data coming from the same study (or cohort) at different time points.

Figure 18. Change in number of antihypertensives change while on medical therapy



Point estimates and 95% confidence intervals from individual studies.

ACEi/ARB use

Two studies reported data on ACEi/ARB use. Both found an increase in the percentage of patients on the drugs from baseline to 1 year. Marcantoni 2012 reported that 79 percent of patients were using ACEi/ARBs at baseline compared to 83 percent at 1 year.[24] Wheatley 2009 reported that 38 percent of patients were using ACEi/ARBs at baseline, while 43 percent were using the drugs at 1 year.[28] See Appendix Tables C.4.14 and C.4.15.

Adverse events

No study reported adverse events related to medication use.

Key Question 2.
Association of patient factors with outcomes

Three studies reported analyses of patient-level predictors of clinical outcomes (**Table 3**). Ritchie 2014,[25] in univariate analyses, found that patients with flash pulmonary edema were significantly more likely to die or, in a separate analysis, to have a cardiovascular event (see Table 3 for list of events), but were not likely to require RRT. Neither rapid kidney function deterioration nor refractory HTN predicted outcomes (see Table 3 for definitions of predictors).

Silva 2008 found that lower GFR was significantly associated with RRT but not death.[84] Proteinuria was a near-significant predictor of RRT, but not death. Sex and history of coronary artery disease were not associated with outcomes.

Key Question 3.
Association of treatment factors with outcomes

Three analyses in two studies examined the association between specific medication treatments and clinical outcomes (**Table 3**). Silva 2008, in multivariable analyses, found that use of beta blockers or angiotensin inhibitors (ACEi or ARB) were not associated with likelihood of death or RRT.[84] In contrast, Hackam et al. in two overlapping analyses of four (Hackam 2008)[86] or six (Hackam 2011)[87] administrative databases, found that angiotensin inhibitor use was associated with reduced cardiovascular events and statin use was associated with reduced cardiorenal events, death and RRT.

Table 3. Independent predictors of selected clinical outcomes in patients receiving medical therapy only

Outcome Study	**Mean F/up (*Metric*)**	**GFR**	**FPE**	**Prot**	**Statins**	**ACEi/ARB**	**Other NS**
Death							
Ritchie 2014	3.8 y (***HR***)		2.19* (1.39, 3.47)				Rapid ΔGFR*, Refractory HTN*
Silva 2008	3 y (***HR***)	0.97 (0.94, 1.002)		NS	0.13 (0.04, 0.44)	NS	Sex, CAD, BB
RRT							
Ritchie 2014†	3.8 y (***HR***)		NS*				Rapid ΔGFR*, Refractory HTN*
Silva 2008	3 y (***HR***)	0.92 (0.88, 0.97)		1.16 (0.99, 1.37)	0.21 (0.07, 0.64)	NS	Sex, CAD, BB
CV Event‡							
Ritchie 2014	3.8 y (***HR***)		3.07* (1.71, 5.51)				Rapid ΔGFR*, Refractory HTN*
Hackam 2008§						0.75 (0.62, 0.91)	
Cardiorenal Event¶							
Hackam 2008/2011§	3.3 y (***HR***)				0.60 (0.53, 0.69)		

*Univariate

† or serum creatinine doubling

‡ Ritchie 2014: Myocardial infarction, acute coronary syndrome, flash pulmonary edema hospitalization, arrhythmia hospitalization, stroke, transient ischemic attack, new onset angina, or coronary revascularization

Hackam 2008: Death, myocardial infarction, or stroke

§ Overlapping studies with data from four (Hackam 2008) or six (Hackam 2011) administrative databases

¶ Myocardial infarction, stroke, heart failure, acute renal failure, dialysis or death

ACEi/ARB = angiotensin converting enzyme inhibitor or angiotensin receptor blockers, BB = beta blocker, CAD = coronary artery disease, F/up = followup, FPE = flash pulmonary edema, GFR = glomerular filtration rate, HR = hazard ratio, Other NS = nonsignificant predictors not otherwise listed, Prot = proteinuria, Rapid ΔGFR = rapid kidney function decline (serum creatinine increase by 20% or 1.14 mg/dL increase in 6 months), Refractory HTN = refractory hypertension (BP >140/90 mmHg on ≥3 medications).

Surgical revascularization

Key points

- 4 studies (3 retrospective, 1 prospective) reported outcomes in patients receiving surgical revascularization. The studies were highly heterogeneous in both their included patients and specific surgical techniques (both within and across studies). The retrospective studies were subject to high risk of bias related to attrition, selective reporting, and lack of adjustment for different lengths of followup. The prospective study was deemed low risk of bias.
- **Mortality**: In 4 studies, mortality ranged from 26 to 36 percent after about 5 years of followup.
- **RRT**: In 2 studies, incident RRT (or combined renal failure outcomes) occurred in 38 and 74 percent of patients at about 5 years of followup.
- **Cardiovascular outcomes**: 1 study reported new-onset angina in 10 percent of patients and coronary revascularization in 8 percent after a mean of 10 years; 6 percent of patients suffered an MI and 4 percent a stroke.
- **Kidney function**: 2 studies reported on kidney function; in one, 43 percent of patients had improved kidney function, 10 percent had worsened kidney function, and 70% of those who were on RRT prior to surgery discontinued dialysis. Mean GFR increased by 7 mL/min after about 5 years (1 study), but mean SCr increased by 0.1 mg/dL at 4 years (in the second study).
- **BP control**: In 4 studies, improved or cured HTN occurred in 53 to 82 percent of patients. 2 studies found large improvements in systolic BP (−53 and −31 mmHg) at 4 to 5 years, but one found a large improvement in diastolic BP (−23 mmHg) and the other study a small, not statistically-significant improvement (−8 mmHg).
- **Adverse events**: 3 studies reported surgery-related adverse events, including postoperative mortality, bleeding, arterial occlusion or thrombosis, infection, and distal embolization.
- **Patient factors**: 2 studies reported on patient-level predictors of clinical outcomes. Both studies found that found that patients with a history of cardiovascular disease, diabetes, worse kidney function, or who were older were at increased risk of all-cause death, cardiovascular death, or either death or RRT. In one study each, higher systolic BP were at lower risk of combined death or RRT but not all-cause death alone, preoperative angina was associated with cardiovascular mortality, and resistive index >0.8 was associated with all-cause death. Race, sex, DBP, and number of antihypertensive medications were not associated with outcomes.
- **Treatment factors**: 1 study addressed differences in treatment factors as predictors of outcomes. Bilateral repair and whether renal artery repair was combined with aortic repair were not associated with death in adjusted analyses.

Key Question 1.
Effects of intervention on outcomes

Four studies reported on primary surgical revascularization for ARAS,[14, 89-91] three of which were used in the previous update. There were three retrospective, nonrandomized

comparative studies of surgery with PTRAS[89-91] and one RCT (versus PTRAS).[14] In total, 880 patients were included. The mean durations of followup ranged from 3.1 to 4.7 years (or up to 5 or 10 years). An additional study reported only significance of differences in outcomes between surgical revascularization and PTRAS and is not included in this section.[27]

Study inclusion criteria incorporated patients with at least 60 percent ARAS,[91] but frequently participants had 70 to 80 percent stenosis or more, by ultrasound or angiography imaging. Inclusion criteria based on degree of stenosis were incomplete or not reported in two studies.[18, 89] The sex distribution varied widely from 43 percent males in Galaria 2005 to 65 percent males in Alhadad 2004. The mean age of the surgical cohorts ranged from 62 to 76 years. Patients with fibromuscular dysplasia (FMD) were either specifically excluded or accounted for a small fraction (<10%) of the total study population. See Appendix Table C.1 for study eligibility criteria and designs.

The indications for operative intervention were to treat ARAS that was causing derangements in BP or kidney function. cardiovascular disease was present in 53 and 90 percent of patients in the two studies that reported it.[90, 91] All baseline SBP measurements were elevated and ranged from a mean of 171 to 200 mmHg. Mean DBP measurements were between 82 and 104 mmHg. The mean serum Cr values were between 1.3 and 2.6 mg/dL See Appendix Tables C.1 and C.3.

Surgical approaches varied according to revascularization needs and available vessels or conduits. Procedures included renal endarterectomy, renal and aortic endarterectomy, and mesenteric (i.e., splenorenal, hepatorenal, iliorenal) or aortorenal bypass procedures. Bypass procedures used native saphenous vein, PTFE (polytetrefluoroethylene), and Dacron grafts to construct the conduits when the native renal artery was not reimplanted. The choice and use of prosthetic grafts were at the surgeon's discretion. In all studies, some patients (9 to 56%) required combined aortic procedures, some of which were done to facilitate the renal bypass, and others were due to concomitant aortoiliac atherosclerotic disease. In one study, secondary operations performed for prior failed endoluminal repairs were included and comprised 10 percent of the total cohort.[91] Specific medication adjuncts used during operative procedures included alprostadil[14] when mentioned. See Appendix Table C.2.3.

The one RCT (Balzer 2009)[14] was of low risk of bias for all Cochrane risk of bias questions. The two retrospective NRCSs (Alhadad 2004 and Galaria 2005)[89, 90] were both adequately representative, but one each were high risk of bias for high attrition, selective outcome reporting, and different lengths of follow-up for different study arms. The prospective study (Cherr 2002)[90] was low risk of bias for all items;

Mortality (study duration 6 months or greater)

In four studies, mortality and long-term survival rates were described after open revascularization.[14, 89-91] In one study, a mortality rate of 26 percent was reported after a mean followup period of 4.5 years.[14] In the other three studies, mortality rates ranged from 26 to 36 percent after a mean followup of 5 years. The majority of late deaths were related to cardiovascular disease in two studies.[89, 90] For details, see Appendix Table C.4.1.

Renal replacement therapy

Progression to ESRD or new requirement for hemodialysis was defined as an endpoint in 2 studies.[90, 91] After a mean follow-up of 4.7 years in one study, 38 percent of survivors required RRT.[90] At 5 years in the second study, the cumulative freedom from RRT or recurrent renal

insufficiency (Cr > 1.5 mg/dL), reported as renal disease-related mortality, was 74 percent (SD 7 percent). [91] See Appendix Table C.4.6.

Cardiovascular outcomes

Only a single study reported long-term cardiovascular outcomes. Cherr 2002 reported new-onset angina in 9.8 percent of patients and coronary revascularization in 8.3 percent after a mean of 10 years; 5.8 percent of patients suffered an MI and 4.4 percent a stroke.[90] See Appendix Table C.4.16.

Kidney function

In one of two studies reporting kidney function outcomes, 43 percent of patients had improved kidney function (including 28 of 40, 70%, who discontinued dialysis), 47 percent had no clinically significant change, and 10 percent had worsened kidney function.[90] In this same study, mean GFR increased by 7 mL/min (95% CI 3.5, 10.7) at a mean of 4.7 years. In another study, mean SCr increased by 0.1 mg/dL (95% CI -0.2, ~0.35) at both 1 and 4 years of followup.[14] See Appendix Tables C.4.4, C.4.6, and C.4.7.

Blood pressure control

Improved or cured HTN was reported in four studies and occurred in 53 to 82 percent of patients.[14, 89-91] Cherr 2002 found decreases in SBP/DBP at a mean of 4.7 years of −53 mmHg (95% CI −80, −26) / −23 mmHg (−35, −11).[90] Balzer 2009 found statistically significant decreases in SBP at 1 and 4 years: at 1 year −21 mmHg (95% CI −38, −4); at 4 years −31 mmHg (95% CI −49, −13). But they found nonsignificant changes in DBP at 1 year (−4 mmHg; 95% CI −14, 6) and 4 years (−8 mmHg; 95% CI −18, 2).[14] See Appendix Tables C.4.10, C.4.12, and C.4.13.

Adverse events (including 30-day mortality)

In three studies, 30-day or in-hospital median mortality was 7 percent (range 0% to 9%).[89-91] Major reported adverse operative events at 30 days included bleeding (8%),[89] arterial occlusion or thrombosis (3.7% and 6.0%),[14, 89] infection (3%),[89] and distal embolization (2%).[89] Immediate reoperations occurred in 4 and 28 percent in two studies.[89, 91] Major nontechnical morbidity events were acute kidney injury (1% to 12%),[89, 90] cerebrovascular events (1%),[89, 90] cardiovascular events (4% to 14%),[89-91] and septicemia (1%).[89, 91] See Appendix Tables C.4.18 and C.4.19.

Key Question 2.
Association of patient factors with outcomes

Two studies reported analyses of patient-level predictors of clinical outcomes.[18, 90] Between the two studies, they found that patients with a history of cardiovascular disease, diabetes, and those with worse kidney function or who were older were at increased risk of all-cause death, cardiovascular death, or either death or RRT (**Table 4**). Specifically, Cherr 2002 found that the HRs for both all-cause death and combined death or RRT were increased independently in patients with lower GFR, and histories of diabetes, myocardial infarction, stroke, and severe aortic occlusive disease.[90] For both outcomes, patients with prior myocardial revascularization were at significantly decreased risk. Older patients were at increased risk of all-cause death, but not combined death or RRT. Those with higher SBP were at lower risk of

combined death or RRT, but not all-cause death alone. Race, sex, DBP, and number of antihypertensive medications were not independently associated with these outcomes. In this study, only the presence of preoperative angina was associated with the risk of cardiovascular mortality (HR 2.18; 95% CI 1.25, 3.84). Crutchley 2009 found that resistive index >0.8 was an independent predictor of all-cause death.[18]

Key Question 3.
Association of treatment factors with outcomes

Cherr 2002 found that bilateral repair did not independently predict death and that perioperative mortality was higher in patients with combined aortic and bilateral repair (6.9%) compared to isolated renal artery repair (0.8%; P=0.01, univariate), but after adjustment for age and clinical CHF, this difference was not statistically significant. [90]

Table 4. Independent predictors of selected clinical outcomes after surgical renal artery repair

Outcome Study	**Mean F/up (*Metric*)**	**Age**	**GFR**	**RI ≥0.8**	**SBP**	**DM**	**CorRevasc**	**Stroke**	**MI**	**Aortic Dz**	**Other NS**
Death											
Cherr 2002	4.7 y (***HR***)	1.22 (1.02, 1.46)	0.60 (0.49, 0.74)		NS	1.75 (1.18, 2.60)	0.60 (0.38, 0.96)	1.52 (1.00, 2.29)	1.48 (1.06, 2.07)	1.49 (1.06, 2.10)	Race, Sex, DBP, Rx
Crutchley 2009*	4.8 y (***HR***)			6.7† (2.6, 17)							
Death or RRT											
Cherr 2002	4.7 y (***HR***)	NS	0.43 (0.34, 0.54)		0.79 (0.67, 0.94)	2.14 (1.15, 3.97)	0.69 (0.45, 1.06)	1.50 (1.02, 2.22)	1.36 (0.99, 1.88)	1.66 (1.19, 2.31)	Race, Sex, DBP, Rx

* Crutchley 2004 was a retrospective comparative study of surgery vs. angioplasty with stent with <100 participants in the surgical arm.[18] Therefore, this studies did not meet eligibility criteria for Key Question 1 for surgical cohorts and was not included there.

† HR for combined surgery and angioplasty with stent groups, described in text and graphically as similar results for both intervention groups.

Aortic Dz = Severe aortic occlusive disease, CHF = congestive heart failure, CorRevasc = coronary revascularization, DBP = diastolic blood pressure, DM = diabetes mellitus, F/up = followup, GFR = glomerular filtration rate (unit used in regression not reported), HR = hazard ratio, LVEF = left ventricular ejection fraction, MI = myocardial infarction, Other NS = nonsignificant predictors not otherwise listed, RI = resistance index, Rx = number of antihypertensive medications, SBP = systolic blood pressure (unit used in regression not reported).

Acute decompensation case reports

Key points

- 20 case reports of patients with acute decompensation of their RAS universally presented patients who, after revascularization (by PTRAS or surgery) improved symptomatically and with improved kidney function and/or BP control. 2 case reports presented patients who, after an episode of acute decompensation, continued medical therapy alone for 10 months in one case and 5 year in the other, but who subsequently had a second episode of decompensation that resulted in clinical improvement. All eight cases who required acute hemodialysis no longer required RRT after revascularization.

None of the comparative or single group studies focused on or explicitly included patients with acute decompensation who have rapidly declining kidney function with possible oliguria or anuria, flash pulmonary edema, and/or intractable malignant HTN. To partially overcome this deficiency, we summarized the 20 most recent case reports of such patients, published between 2006 and 2014 (Table 5).[92-111]

The patients ranged in age from 49 to 83 years old (median 69.5); 13 were women. Most commonly, patients (n=13) had new onset dyspnea, orthopnea, CHF or flash pulmonary edema symptoms. Nine patients were described as having difficult to control, rapidly accelerating, or malignant HTN. Seven patients had acute renal failure or rapid rises in SCr or falls in GFR; four described oliguria or anuria; and eight of the patients required hemodialysis at some point. Other presenting symptoms included angina, chest pain, or acute myocardial infarction, peripheral edema, nausea and vomiting, malaise and other nonspecific symptoms. Among the six patients with reported data, presentation GFR ranged from 17 to 45 mL/min. Among 19 patients, the presentation SCr ranged from 1.1 to 9.3 mg/dL; in seven cases, there was a description of a rapid rise in SCr over the proceeding days, which usually led to hemodialysis. Presentation BP was substantially elevated in all but one case (and one additional case whose BP was not reported), ranging from 170/90 mmHg on one antihypertensive drug to 220/100 mmHg on 11 drugs. Five patients were on no or one antihypertensive drug at presentation. The lowest presentation BP was 120/70 mmHg on three drugs (in a patient who was being medically treated for RAS and presented requiring hemodialysis).

All but one patient were found to have high grade stenosis (of at least 80% or described as critical or some other term) in at least one renal artery. High grade stenosis in both renal arteries (or equivalent) was reported in 10 of 18 patients.

Two of the 10 patients refused PTRAS on first presentation and were treated medically. One of these cases (reported by Li 2012) remained stable for 4 or 5 years but after a second episode of decompensation had bilateral PTRAS.[99] The second case (Islam 2009) did not have true RAS decompensation at first presentation since her rapid rise in SCr was secondary to ramipril treatment.[101] However, 10 months later, the patient decompensated and suffered a myocardial infarction and required hemodialysis. She also then had PTRAS. All other patients had PTRAS or surgical revascularization (2 cases) within one or two weeks of initial decompensation.

Followup after revascularization occurred from hospital discharge to 5 years (median 5 months). Only seven of the cases reported outcomes 1 year or more after revascularization. Among the 18 cases that reported followup kidney function, all patients had improved (or stable,

one patient) kidney function. All eight cases who required acute hemodialysis no longer required RRT after revascularization. Among 16 cases with followup data, BP was improved in 15; in one case[99] (Li 2012), SBP was increased compared with presentation but DBP was stable; the number of medications the patient was on was not reported. In seven of eight cases with data on the number of antihypertensive medications at presentation and followup, the number of drugs was reduced or the same (one case) at followup with a lower BP. One patient was on one drug at presentation and had controlled BP at 6 week followup on three drugs. One case report (Alonso 2013) did not report kidney or BP followup but reported only that the patients pulmonary edema symptoms had fully resolved at 3 months.[95] For all cases who presented with flash pulmonary edema, CHF, or dyspnea, it was stated or implied that symptoms were fully resolved without recurrence at followup.

In summary, a review of the 20 most recently published case reports of management of patients with ARAS with acute decompensation—as manifested by rapid worsening of kidney function, recent severe or difficult to control HTN, flash pulmonary edema, or related symptoms—found that all patients improved after revascularization, almost always with PTRAS. One of the case reports described a patient who refused recommended revascularization for her acute RAS decompensation. She was managed successfully for 5 years until she had a second decompensation at which point she was treated with PTRAS. Overall, the case reports all report clinically successful revascularizations in patients with acute decompensation.

Table 5. Case Reports
Each row = individual patient

Study, Year PMID	Decompensation Description	Comorbidities	Acuity (Time)	o Age, y (Sex) • % Stenosis	Pre-Tx ▪ GFR [SCr] ❖ Pulm Ed?	Pre-Tx ➢BP ● No. Rx	Intervention	Followup Time	Response ▪ GFR [SCr] ❖ Pulm Ed?	Response ➢BP ● No. Rx
Komatsu, 2014 None	RI, HTN	DM, PVD		o 65 y (M) • L 90%	▪ [1.10] ❖	➢156/98 ●	PTRAS L	In-hospital	▪ [0.97] ❖	➢122/73 ●
Demming, 2013 23673780	Acute chest pain and progressive dyspnea	DCM, MR, MetS, COLD	7 d	o 83 y (F) • L "high-grade"; R hypoplasia	▪ 23 [2.2] ❖ Yes	➢220/100 ● 11 Rx	PTRAS L	1.5 y	▪ 34 [1.55] ❖	➢ ● 5 Rx
Ishida, 2013 23473081	Severe HTN, rapidly worsening RI	CRF		o 69 y (M) • R 99%	▪ [6.94] ❖ Severe LE edema	➢180/90 ● 5 Rx	PTRAS R	1 mo	▪ [4.0] ❖ Edema ameliorated	➢135/70 ● 3 Rx
								1 y	▪ [3.8] ❖	➢135/65 ● 1 Rx
Alonso, 2013 22944546	Sudden acute dyspnea	HTN, DM, no CAD	2 (FPE x 3 in 6 mo)	o 73 y (F) • B critical	▪ ❖ Yes	➢194/115 ● 4 Rx	PTRAS B	3 mo	▪ ❖ None	➢ ●
Chrysochou, 2013 22262735	FPE x 3, poorly controlled HTN	LVH, claudication, no CAD	12 mo	o 65 y (F) • B 85%	▪ 26 [] ❖ Yes (NYHA II)	➢161/80 (ABPM) ● 6 Rx	PTRAS	2 wk	▪ ❖ No (2 flights*)	➢101/57 ● 4 Rx
								4 mo	▪ 34 [] ❖	➢ ● 1 Rx
								1 y	▪ ❖	➢129/71 ● 3 Rx
Noce 2012 23427756	Refractory HTN, ARF	No HTN	Recent ()	o 51 y (M) • R 85%; L 75%	▪ 28 [5.78] ❖ No (LVH, no edema)	➢190-220 / 100-130 ● 2 Rx	PTRAS B	30 d	▪ [2.8] ❖	➢150/85 ● 2 Rx
								5 y	▪ 65 [1.5] ❖	➢120/80 ● 1 Rx
Li, 2012 21558176	FPE, ACS (in 2002)			o 73 y (F) • R 82% L 87%	▪ 17 [2.9] ❖ Yes	➢ ● 0 Rx (implied)	Medical (refused PTRAS)	4 y	▪ [1.8-2.0] ❖ No	➢154/69 ● 3 Rx
	FPE, ARF (in 2007), RRT †			o ~78 • B "tight"	▪ HD ❖ Yes	➢120/70 ● 3 Rx (implied)	PTRAS B	3.5 y	▪ 30 [1.7] Off RRT ❖ AFib/CHF	➢140/72 ●

Study, Year PMID	Decompensation Description	Comorbidities	Acuity (Time)	o Age, y (Sex) • % Stenosis	Pre-Tx ▪ GFR [SCr] ❖ Pulm Ed?	Pre-Tx ➢BP ● No. Rx	Intervention	Followup Time	Response ▪ GFR [SCr] ❖ Pulm Ed?	Response ➢BP ● No. Rx
Navaravong, 2011 21855421	CHF Sx, ARF, Uncontrolled HTN	L occluded, R 70%, CAD, CKD IV (SCr 1.6), HTN, AAA		o 79 y (M) • R 99%; L 100%	▪ [5.4], anuric ❖ Yes	➢170/90 ● 1 Rx	PTRAS R	4 d	▪ [1.5] ❖ Yes	➢Improved ●
George, 2011 21566313	Rest angina, acute LVF & FPE, uncontrolled HTN		>2 d	o 70 y (F) • (bilat)	▪ 45 [3.0] ❖ Yes	➢210/110 ● 4 Rx	PTRAS R	D/C	▪ 63 [1.6] ❖	➢"well-controlled ● 2 Rx
								2 mo	▪ [1.3] ❖	➢ ●
Kindo 2011 21118836	FPE	CHF, PAD, Heart transplant, HTN		o 60 y (M) • (L no function)	▪ [2.5] ❖ Yes	➢190/100 ●	Hepatorenal bypass R	5 d	▪ [2.0] ❖	➢Controlled ●
								3 y	▪ [1.6] ❖ No	➢ ●
Islam, 2009 19808722	SCr rise on ramipril	(SCr 1.2)	Acute	o ~59 (F) • B Severe	▪ [2.0] ❖	➢ ●	Medical (refused PTRAS)	10 mo	▪ (1.5-2.5) ❖ Yes	➢ ●
	SOB, FPE, AMI, RRT (10 mo later)‡	Uncontrolled HTN, Acute CHF‡	10 d	o 60 y • 100% (bilat)	▪ [4.0→7.6, HD] ❖ Yes	➢180/92 ● 5 Rx	PTRAS B	3 d	▪ [2.1] Off RRT ❖ "no recurrence in followup"	➢ ●
Kanamori, 2009 19726830	Dizziness, Severe HTN, ARF, RRT		30 d	o 72 y (F) • R 100%; L 90%	▪ [1.2→6.7, HD] ❖ Yes	➢190/100 ● 1 Rx (implied)	PTRAS B		▪ [0.8] Off RRT ❖ No	➢140/90 ●
Dippel, 2009 19652259	Accelerated HTN	CAD, TIA		o 74 (F) • R 40-50% L 80%	▪ 30 [1.3] ❖ No	➢200/100 ● 3 Rx	PTRAS L (with DEP)	30 d	▪ ❖	➢90/46 ● 2 Rx
								1 y	▪ ❖	➢100/60 ● 2 Rx
Dziemianko, 2009 19379457	ARF, RRT, HTN crisis, Dyspnea, LE edema	None		o 53 y (M) • R 75%; L 95%	▪ [3.6→HD] ❖ Yes	➢260/150 ● 0 Rx (implied)	PTRAS L#	6 mo#	▪ [1.5] Off RRT ❖ No	➢144/91 (ABPM) ●

Study, Year PMID	Decompensation Description	Comorbidities	Acuity (Time)	o Age, y (Sex) • % Stenosis	Pre-Tx ▪ GFR [SCr] ❖ Pulm Ed?	Pre-Tx ➢BP ● No. Rx	Intervention	Followup Time	Response ▪ GFR [SCr] ❖ Pulm Ed?	Response ➢BP ● No. Rx
Chrysochou, 2009 18045711	Oligoanuria, RRT, malaise, breathlessness	RAS (50-75% L), DM, HTN (199/89)	3 d	o 73 y (F) • R 100%, L >95%	▪ [8.0→HD] ❖ Yes	➢221/80 ● 5 Rx	PTRAS L	3 d	▪ [2.6] Off RRT ❖	➢ ●
								8 mo	▪ 26 [2.0] ❖	➢ ●
Campbell, 2008 18335782	N/V/D, Low back pain, anuria, RRT	HTN	5 d	o 49 y (F) • R ≥60% • L <60%	▪ [9.3→HD] ❖ No	➢188/76 ● 1 Rx	Aortorenal artery bypass R	6 d	▪ [1.8] Off RRT ❖ No	➢ ●
								6 wk	▪ [1.5] ❖ No	➢Controlled ● 3 Rx
Wykrzykowska, 2008 18174627	FPE (ventilation)	Giant cell arteritis, HTN, PVD		o 81 y (F) • R mild; L severe	▪ [2.7] ❖	➢200/ ● 5 Rx	PTRAS L	5 mo	▪ [1.4] ❖ No	➢160/ ●
	CHF, Severe HTN (6 mo later)§			o 81 or 82 y • R severe; L patent	▪ ❖ Yes	➢Severe ●	PTRAS R		▪ ❖ No	➢Improved ●
Kuznetsov, 2007 17703833	Weakness, dyspnea, chest discomfort, N/V→Anuria, RRT	HTN, CVA, CAD, CHF, Aortic stenosis (SCr 1.5)	2 wk	o 75 y (F) • B critical	▪ [2.8→6.5→HD] ❖ Yes	➢210/110 ● 3 Rx	PTRAS B (with DEP)	D/C	▪ [1.9] Off RRT ❖ No	➢115-147/ 53-72 ● 3 Rx
								4 mo	▪ [1.7] ❖	➢ ●
Kumar, 2006 16941797	Recurrent breathlessness, FPE x 4	CAD, No HTN	1 mo	o 58 y (M) • L 99% R 90%	▪ [1.7] ❖ Yes	➢160-170 / 100-110 ● 2 Rx	PTRAS B	3 mo	▪ [1.2] ❖ No	➢ ●
George, 2006 16521653	Dyspnea, oliguria, RRT, anasarca, orthopnea	Aortoarteritis, L nephrectomy (occluded RA)	2 wk	o 51 y (F) • R 100%	▪ [3.6→HD] ❖ Yes	➢190/110 ●	PTRAS R	2 d	▪ [1.0] Off RRT ❖ No	➢ ● 2 Rx
								3 wk	▪ Stable ❖	➢Stable ● 2 Rx

* Exercise tolerance improved to ~50 yards and she was able to climb 2 flights of stairs before needing to stop.
† Second acute episode in same woman about 5 years later.
‡ Second episode 10 months later
# R PTRAS placed at 6 months. 6 months subsequently "kidney function remained normal and blood pressure normalized."
§ Second episode 6 months later

AAA = abdominal aortic aneurysm, ABPM = 24 hour ambulatory blood pressure monitoring, ACS = acute coronary syndrome, AFib = atrial fibrillation, AMI = acute myocardial infarction, B = bilateral, BP = blood pressure (in mmHg), CHF = congestive heart failure, CKD IV = chronic kidney disease stage IV, COPD = chronic obstructive pulmonary disease, CRF = chronic renal failure, D/C = hospital discharge, DCM = dilated cardiomyopathy, DEP = distal embolic protection device, DM = diabetes mellitus, FPE = flash pulmonary edema, GFR = glomerular filtration rate (in mL/min/m^2), HD = hemodialysis, HTN = hypertension, K = potassium (in mg/dL), L = left renal artery, LE = lower extremity, LVF = left ventricular failure, M/F = male or female, MetS = metabolic syndrome, MR = mitral regurgitation, N/V/D = nausea vomiting and diarrhea, nd = no data, NYHA = New York Heart Association class, PAD = peripheral artery disease, Plasty = angioplasty, Pre-Tx = pre-treatment (during acute decompensation), PTRAS = percutaneous transluminal renal angioplasty with stent, Pulm Ed = flash pulmonary edema, PVD = peripheral vascular disease (not including renal artery disease), R = right renal artery, RA = renal artery, RCA = right coronary artery stenosis, RI = “renal impairment”, RRT = renal replacement therapy (dialysis) [required], Rx = antihypertensive medications required, SCr = serum creatinine (in mg/dL), Sx = symptoms, TIA = transient ischemic attack.

Strength of evidence across study designs

As summarized in **Table 6**, for all outcomes, the strength of evidence is low regarding the relative benefit of *PTRAS versus medical therapy alone* for patients with ARAS, across both comparative and noncomparative studies.

Overall, there is a low strength of evidence that there is no difference in clinically important outcomes (death, cardiovascular events, RRT), but this conclusion is most applicable to those patients for whom there is clinical equipoise between the two treatments (patients for whom no clear benefit of revascularization is perceived). The RCTs generally found no clear differences in rates of clinically important outcomes but had the important limitation of low applicability to typical patients for whom PTRAS is being recommended, since these patients were excluded from the trials either by design or because of difficulty recruiting them into trials that might disallow revascularization. The NRCSs were less consistent, but provided less reliable estimates of comparative effect due to inadequate adjustment for fundamental differences in patients who are chosen for revascularization and those who remain on medical therapy. For these reasons, the NRCSs were deemed to not provide sufficiently strong evidence to upgrade the strength of evidence derived from the RCTs. Likewise, the single-intervention cohorts are highly heterogeneous across studies in their patient populations and their estimates of outcome rates. It is highly unlikely that the patients in the PTRAS studies are comparable to those in the (many fewer) medical therapy studies.

Overall, there is low strength of evidence that kidney function and BP control may be improved in patients who undergo PTRAS, based on comparative studies and the indirect comparison between cohorts of patients who had PTRAS or continued medical therapy.

Likewise, overall, there is low strength of evidence that clinically important adverse events are more common, though rare, related to PTRAS than medical therapy alone; however, studies generally failed to report medication-related adverse events.

As summarized in **Table 7**, for all outcomes, there is insufficient evidence to determine the strength of evidence regarding the relative benefit of *open surgery versus medical therapy alone* for patients with ARAS, across both comparative and noncomparative studies. There is only a single comparative study of open surgery versus medical therapy and few single-group studies of surgery. These did not provide sufficient evidence to adequately assess the relative difference in outcomes between the interventions.

As summarized in **Table 8**, for each outcomes, the strength of evidence is insufficient or low regarding the relative benefit of *PTRAS versus surgery* for patients with ARAS, across both comparative and noncomparative studies. A single RCT and three poorly reported NRCS evaluated this comparison. There is low strength of evidence of no difference in mortality or BP control between the two revascularization approaches, but inadequate evidence for other outcomes of interest.

Table 6. Angioplasty with stent vs. medical therapy alone for the treatment of ARAS: Strength of evidence

Outcome	SoE Grade	Design No. Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Death	Low	RCT: 4 NRCS: 4 Cohort PTRAS: 31 Cohort Rx: 10	Medium	RCT: Direct Other: Indirect	RCT: consistent All: inconsistent	Imprecise	Undetected	Important*	Comparative studies: No difference Single arm studies: Broadly similar
RRT	Low	RCT: 3 NRCS: 0 Cohort PTRAS: 7 Cohort Rx: 7 Case: 18	Medium	RCT: Direct Other: Indirect	RCT: consistent All: inconsistent	Imprecise	Undetected	Important*	RCT: No difference Single arm studies: Broadly similar Case: RRT averted with revascularization
CV event	Low	RCT: 2 NRCS: 0 Cohort PTRAS: 12 Cohort Rx: 9 Case: 18†	Medium	RCT: Direct Other: Indirect	RCT: consistent All: inconsistent	Imprecise	Undetected	Important*	RCT: No difference Single arm studies: Unclear Case: CV symptoms resolved immediately with revascularization
Kidney function	Low	RCT 1 NRCS: 3 Cohort PTRAS: 27 Cohort Rx: 10 Case: 18	Medium	RCT: Direct Other: Indirect	RCT: consistent All: consistent	Imprecise	Undetected	Important*	Comparative: Better kidney function after PTRAS Single arm studies: PTRAS better Case: Improvement with revascularization
BP control	Low	RCT: 4 NRCS: 7 Cohort PTRAS: 30 Cohort Rx: 13 Case: 18	Medium	RCT: Direct Other: Indirect	Comparative: inconsistent All: consistent	Imprecise	Undetected	Important*	Comparative: Inconsistent, but overall possibly favoring PTRAS Single arm studies: PTRAS better Case: Improvement with revascularization
Adverse events	Low	RCT: 2 NRCS: 1 Cohort PTRAS: 19 Cohort Rx: 0	Medium	RCT: Direct Other: Indirect	Consistent	Imprecise	Suspected	Important‡	Severe AE rare, but occurred only in PTRAS studies. Single arm studies: reported only in PTRAS studies

AE = adverse events, Case = case reports, CV = cardiovascular, N = number of study participants, No. = number, NRCS = nonrandomized comparative studies, PTRAS = percutaneous transluminal renal angioplasty with stent placement, RCT = randomized controlled trials, RRT = renal replacement therapy, Rx = medical therapy alone, SoE = strength of evidence.

* RCTs of limited applicability to typical patients choosing PTRAS. NRCSs inadequately adjusted. Single arm studies analyzed poorly comparable cohorts of patients.
† Congestive heart failure / pulmonary edema symptoms and angina
‡ Noncomparable adverse events between PTRAS and medical therapy. Poorly reported.

Table 7. Surgery vs. medical therapy alone for the treatment of ARAS: Strength of evidence

Outcome	SoE Grade	Design No. Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Death	Insufficient	RCT: 1 NRCS: 0 Cohort Surgery: 4 Cohort Rx: 10	Low	RCT: Direct Other: Indirect	Single comparative study	Imprecise	Undetected	Important*	Comparative study: No difference Single arm studies: Broadly similar
RRT	Insufficient	RCT: 1 NRCS: 0 Cohort Surgery: 2 Cohort Rx: 10 Case: 2	Low	RCT: Direct Other: Indirect	Single comparative study	Imprecise	Undetected	Important*	RCT: No difference Single arm studies: Broadly similar Case: RRT averted with revascularization
CV event	Insufficient	RCT: 0 NRCS: 0 Cohort Surgery: 1 Cohort Rx: 10 Case: 2	Low	RCT: none Other: indirect	No comparative studies	Imprecise	Not reported	Important*	RCT: No data Single arm studies: Unclear Case: CV symptoms resolved immediately with revascularization
Kidney function	Insufficient	RCT: 1 NRCS: 0 Cohort Surgery: 1 Cohort Rx: 10 Case: 2	Low	RCT: Direct Other: Indirect	Single comparative study	Imprecise	Undetected	Important*	RCT: No difference Single arm studies: PTRAS better Case: Improvement with revascularization
BP control	Insufficient	RCT: 1 NRCS: 0 Cohort Surgery: 4 Cohort Rx: 10 Case: 2	Low	RCT: Direct Other: Indirect	Single comparative study	Imprecise	Undetected	Important*	RCT: No difference Single arm studies: PTRAS better Case: Improvement with revascularization
Adverse events	Insufficient	RCT: 1 NRCS: 0 Cohort Surgery: 3 Cohort Rx: 10 Case: 2	Low	RCT: Direct Other: Indirect	Single comparative study	Imprecise	Suspected	Important‡	RCT: No data Single arm studies: reported only in surgery studies

AE = adverse events, Case = case reports, CV = cardiovascular, N = number of study participants, No. = number, NRCS = nonrandomized comparative studies, PTRAS = percutaneous transluminal renal angioplasty with stent placement, RCT = randomized controlled trials, RRT = renal replacement therapy, Rx = medical therapy alone, SoE = strength of evidence.

* RCT of limited applicability to typical patients choosing PTRAS. Single comparative study only. Single arm studies analyzed poorly comparable cohorts of patients.
‡ Noncomparable adverse events between surgery and medical therapy. Poorly reported.

Table 8. Angioplasty with stent vs. surgery for the treatment of ARAS: Strength of evidence

Outcome	SoE Grade	Design No. Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Death	Low	RCT: 1 NRCS: 2 Cohort PTRAS: 31 Cohort Surgery: 4	Low	RCT: Direct Other: Indirect	RCT: consistent All: consistent	Imprecise	Undetected	Important*	Comparative studies: No difference Single arm studies: Broadly similar
RRT	Low	RCT: 0 NRCS: 1 Cohort PTRAS: 31 Cohort Surgery: 2 Case: 20	Low	RCT: Direct Other: Indirect	RCT: no data All: consistent	Imprecise	Undetected	Important*	Comparative: No difference Single arm studies: Broadly similar Case: Similar outcomes
CV event	Low	RCT: 0 NRCS: 0 Cohort PTRAS: 31 Cohort Surgery: 1 Case: 20	Low	RCT: none Other: Indirect	RCT: no data All: inadequate data	Imprecise	Undetected	Important*	Comparative: No difference Single arm studies: Unclear Case: Similar outcomes
Kidney function	Low	RCT: 1 NRCS: 1 Cohort PTRAS: 31 Cohort Surgery: 1 Case: 20	Low	RCT: Direct Other: Indirect	RCT: consistent All: inconsistent	Imprecise	Undetected	Important*	Comparative: No difference Single arm studies: PTRAS better Case: Similar improvement
BP control	Low	RCT: 1 NRCS: 2 Cohort PTRAS: 31 Cohort Surgery: 4 Case: 20	Low	RCT: Direct Other: Indirect	RCT: consistent All: inconsistent	Imprecise	Undetected	Important*	Comparative: No difference Single arm studies: PTRAS better Case: Similar improvement
Adverse events	Low	RCT: 1 NRCS: 1 Cohort PTRAS: 31 Cohort Surgery: 3	Low	RCT: Direct Other: Indirect	Consistent	Imprecise	Suspected	Important‡	Severe AE rare with both interventions, requiring additional procedures.

AE = adverse events, Case = case reports, CV = cardiovascular, N = number of study participants, No. = number, NRCS = nonrandomized comparative studies, PTRAS = percutaneous transluminal renal angioplasty with stent placement, RCT = randomized controlled trials, RRT = renal replacement therapy, Rx = medical therapy alone, SoE = strength of evidence.

* RCTs of limited applicability to typical patients choosing PTRAS. NRCSs inadequately adjusted. Single arm studies analyzed poorly comparable cohorts of patients.
† Congestive heart failure / pulmonary edema symptoms and angina
‡ Noncomparable adverse events between PTRAS and medical therapy. Poorly reported.

Discussion

This review included 76 studies that evaluated medical therapy, PTRAS, or surgical revascularization since approximately 1995 in patients with ARAS, in addition to the 20 most recent case reports of revascularization in patients with acute decompensation related to ARAS. Among these, only five RCTs compared the two most common interventions in current practice, namely PTRAS (with continued medical therapy) and medical therapy alone. However, in only three of these (CORAL, RASCAD, and Bax 2009)[15, 17, 24] were all patients treated with "aggressive" or "optimal" medical therapy, namely antihypertensives, a statin, and an antiplatelet drug.

Summary

The trials of PTRAS versus medical therapy found no difference in long-term outcomes in patients for whom there was equipoise between the two interventions. These results generalize to patients who are similar to those enrolled in the RCTs—patients for whom revascularization is not considered necessary in current clinical practice (since the patients and their clinicians had to agree to the possibility of not having PTRAS)—but not necessarily to the majority of patients undergoing PTRAS, since, in clinical practice, there is often a strong belief that PTRAS is superior to continued medical therapy alone. It remains unclear whether PTRAS (with continuation of medical therapy) offers a clinical benefit to patients currently indicated to have PTRAS compared with remaining on medical therapy alone. Arguably, given the results of the RCTs, an important question is which factors predict patient response to each intervention. In populations such as those included in the RCTs, some patients may benefit more from medical therapy only and some from PTRAS plus medical therapy, resulting in no difference overall. More generally, for all patients it is important to know which factors would predict better outcomes with PTRAS than medical therapy.

Given the limitation of who could be recruited into trials of PTRAS versus medical therapy, well-analyzed, high-quality observational studies could have yielded some better insights into whether patients who receive PTRAS based on standards of practice actually do better because of the intervention. Such studies would have to be multicenter and from practices that have different thresholds or criteria for which patients have PTRAS to allow for an overlap across the centers in patients who likely would have continued medical therapy alone at more conservative centers but would have had PTRAS at more aggressive centers. It can be argued that these data should then be analyzed by propensity score adjustment, where the outcomes are adjusted for each patient's likelihood of having received PTRAS. Such an analysis could better account for differences between groups due to fundamental differences in treatment assignment (who gets which treatment) and may come close to estimating the associations that theoretically could be found in a RCT in patients who are commonly thought to "require" PTRAS.[112-114] However, none of the comparative observational studies performed such an analysis or even sufficiently adjusted their analyses to overcome the inherent clinical differences in patients who go ahead with invasive revascularization and those who continue with medical therapy alone. Therefore, the studies continue to provide an inadequate evaluation of whether the general population of patients for whom PTRAS is thought to be indicated truly benefit from the procedure in terms of the most important patient-centered outcomes of death, RRT, and cardiovascular events.

Subgroup and predictor analyses

Nevertheless, there is clearly a subset of patients who have improved kidney function and improved BP control after PTRAS compared to their kidney and BP status while on medical therapy alone (pre-PTRAS). After PTRAS, on average, GFR did not improve, but BP generally decreased by about 10 to 30 mmHg at the same time that the number of antihypertensive medications used decreased by about 0.5 drugs. In different cohorts of patients, those remaining on medical therapy alone generally had BP decreases by an average of about 5 to 10 mmHg without significant changes in the number of antihypertensive medications used. But there is a strong indication of heterogeneity of treatment effect occurring, such that some patients benefit but others fail to. After PTRAS, in most studies, between 10 and 20 percent of patients have kidney function improvement and about 40 to 80 percent have BP improvement.

The case reports of patients who presented with acute decompensation of their ARAS—namely rapidly developing uncontrollable HTN, acute kidney injury, new onset dialysis, flash pulmonary edema, or other signs of decompensating CHF—provide anecdotal evidence that this subset of patients can benefit from renal artery revascularization. Certainly, these case reports are not an unbiased sample of such patients. It is striking that all case reports were patients who had successful outcomes, but it is highly unlikely that all patients with acute decompensation benefit from revascularization; particularly those already on dialysis. Descriptions of patients who failed to benefit would be interesting and could potentially yield some insights to predict who may not benefit. Better, a study that includes an unbiased sample of these patients is needed.

Analyses of predictors of outcomes after PTRAS yielded generally inconsistent or not particularly illuminating findings. The trials (CORAL and ASTRAL)[17, 28] failed to find factors that describe a putative subset of patients who benefited from PTRAS. The one observational study that reported an analysis of predictors with terms describing the interaction between the predictor factors and intervention (Ritchie 2014) found that patients presenting with flash pulmonary edema with both rapidly declining kidney function and refractory HTN (but not either of the latter conditions alone) had reduced relative rates of death compared with those treated medically. [25] In the observational studies of PTRAS, the most consistent findings were that patients with worse kidney function or BP were most likely to have improvement in those outcomes after PTRAS; though to what degree this is due to regression to the mean is unclear. Studies were not consistent regarding whether patients with bilateral stenosis had significantly different effects on kidney function or BP than patients with unilateral disease. Regarding clinical event outcomes, the most consistent finding was that people with worse cardiovascular risk factors or history of cardiovascular disease were more likely to die or have future cardiovascular events, consistent with what would be found in the general population regardless of treatment.

The data on whether different intervention techniques (such as different stent types or use of brachytherapy or embolization protection devices) improve outcomes remains sparse, but does not support any specific PTRAS technique.

Comparison with prior Comparative Effectiveness Review

Since 2007, the comparative study evidence has improved sufficiently to allow us to focus on PTRAS versus medical therapy (and surgery). In the 2006 and 2007 reports, because of limited evidence, studies of PTRA (without stenting) or of either PTRAS or PTRA were included as proxies for evaluation of PTRAS. With the publication of trials of PTRAS

specifically, we were able to exclude these studies. Thus, of the two RCTs and eight nonrandomized comparative studies of PTRAS or PTRA included in the 2006 review, only one reported on an analysis of interest to the current review.[21] The evidence regarding the principal comparison of interest—PTRAS versus medical therapy—is, therefore, based on almost all recently published studies. Due to the limitations of the new studies, though, the conclusions about the relative benefits and harms of the intereventions remain weak. It might be noted that, in contrast with the current review, the strength of evidence in the original reports was graded as "acceptable" for some outcomes. The apparent downgrading of the evidence can be explained by application of the more rigorous, current methodology for evaluating strength of evidence than was used in 2006 and 2007. Similarly, only one of the other comparative studies (of surgery vs. medical therapy[27]) was included in the original reviews.

The evidence from single-group studies was also mostly from newly published studies since 2007. This includes 35 of 63 single-group studies of PTRAS, 13 of 17 single-group studies of medical therapy, and one of four surgical single-group studies. Similarly, among studies providing evidence for Key Questions 2 and 3 (patient and treatment characteristics as predictors of outcomes) from single intervention groups, 12 of 20 PTRAS studies, both medical therapy studies, and one of the two surgical studies are newly published. While there is currently more evidence about more predictors and outcomes, the studies still do not provide conclusive evidence to support which patients should (or should not) have revascularization over continued medical therapy alone.

Possible reasons for inconclusive evidence, including study limitations

There are several plausible reasons why renal artery revascularization may not substantially improve clinical outcomes in individual patients. Primarily, there is substantial overlap in the etiologic factors of aortorenal vascular disease, parenchymal kidney disease, and cardiac and cerebral vascular diseases. While diabetes mellitus, dyslipidemia, and elevated BP are associated with atherosclerotic narrowing of the renal arteries and consequent worsening of BP and kidney function, they are also independently associated with direct kidney injury. Overcoming the renal artery lesion may fail to improve HTN or kidney function, which may be mediated not only by ARAS but also by underlying kidney disease (due to parenchymal disease or prior irreversible damage from ARAS). The underlying pathophysiology and atherosclerotic milieu present in individuals with ARAS is unchanged by PTRAS. Therefore, continuation of aggressive medical therapy (antihypertensives, statins, and antilipid drugs) is still necessary after PTRAS to minimize risk of cardiovascular events (including cardiac, stroke, kidney, aortic aneurysm, and peripheral vascular disease outcomes). Theoretically, some reduction in antihypertensive medication dose or number of drugs may be feasible after PTRAS due to better BP control, but this is not borne out by the limited evidence.

A number of issues complicate the process of making decisions both for individual patients and for populations of patients. For one, the exact definition of ARAS varies depending on which diagnostic test is used, what threshold for stenosis is preferred, what degree of either resistant HTN or of kidney damage is required, and whether other evidence of atherosclerotic disease is present. Furthermore, the definition and relative importance of these items have been and continue to change as new diagnostic tests are used or existing tests are refined, as definitions of chronic kidney disease change, as treatments for HTN improve, and as techniques and modalities of surgical and percutaneous interventions change and, presumably, improve. In

addition, for individual patients, the evaluation of RAS may be complicated by the risks, difficulties, and expense of the diagnostic tests, including acute kidney injury due to contrast dye. In clinical practice, the primary indication for performing renal angiography or other testing to diagnose ARAS is to determine whether a given patient should have revascularization. Patients who are not candidates for revascularization will not benefit from testing since medical therapy—antihypertensives as tolerated, antilipid drugs, and antiplatelet drugs—is identical with or without confirmation of the diagnosis.

For individual patients and their clinicians, the question of what the preferred treatment for ARAS may be is fraught with difficulties largely related to the frequent frailty of these patients and the known complications from any of the interventions. These patients are generally elderly, often with severe cardiovascular disease, including atherosclerosis and diastolic left ventricular dysfunction, often with moderate or severe chronic kidney disease, and with diabetes. Each of the antihypertensive agents carries substantial risks of bothersome and dangerous adverse events, which may be more likely or serious when multiple drugs are used. These drugs in general need to be taken lifelong and may only prevent further worsening of cardiovascular or kidney disease, as opposed to reducing the severity of existing disease. Invasive interventions, whether open or percutaneous, however, also carry risks of immediate death, cardiovascular events, acute and permanent kidney injury, and pain or other effects on quality of life. Also, the procedure may not carry any noticeable benefit to patients, in that they are likely to continue to require antihypertensive medications and may have no survival benefit or lessened risk of cardiovascular events or RRT. Thus the relative overall effectiveness of angioplasty and continued aggressive medical therapy for most patients with ARAS remains unclear. For some patients with acutely worsening kidney or cardiovascular function, anecdotal evidence strongly suggests a benefit from revascularization.

Another limiting issue was that adverse event reporting was generally sparse and not reported in a consistent manner. While there was little indication of ascertainment bias in regards to long-term clinical outcomes, adverse event reporting was different for different interventions. Across all studies, both comparative and single arm, studies reported on adverse events related to PTRAS but not medical therapy. Revascularization studies tended to focus exclusively on periprocedure complications, without considering any RAS-related drug adverse events.

Conclusions

Overall, the evidence suggests that PTRAS does not provide a benefit over medical therapy alone in patients for whom there is equipoise between the two intervention approaches. But observational studies suggest that patients with greater indications for PTRAS—specifically worse kidney function (variously defined), higher BP (also variously defined), or flash pulmonary edema—may be more likely to have improved kidney function and BP with PTRAS. Although it still remains unknown whether these “high risk” patients have benefits in survival and avoiding cardiovascular events and RRT, compared to remaining on medical therapy. Anecdotal evidence confirms that some patients with acute decompensation due to ARAS benefit clinically from revascularization. Future studies or reanalyses of existing databases are needed to determine the relative effectiveness of PTRAS and medical therapy in patients for whom PTRAS is currently commonly recommended. Since patients who receive PTRAS are generally different in their health status from those who remain on medical therapy alone, propensity score adjustment of large observational datasets may allow for relatively unbiased analyses of these patients by properly accounting for these differences.

References

1. Safian RD, Textor SC. Renal-artery stenosis. The New England journal of medicine. 2001 Feb 8;344(6):431-42. PMID: 11172181.
2. de Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. Journal of hypertension. 2009 Jul;27(7):1333-40. PMID: 19365285.
3. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. Jama. 2003 May 21;289(19):2560-72. PMID: 12748199.
4. Taylor AT, Jr., Fletcher JW, Nally JV, Jr., et al. Procedure guideline for diagnosis of renovascular hypertension. Society of Nuclear Medicine. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 1998 Jul;39(7):1297-302. PMID: 9669414.
5. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2004 May;43(5 Suppl 1):S1-290. PMID: 15114537.
6. Kalra PA, Guo H, Gilbertson DT, et al. Atherosclerotic renovascular disease in the United States. Kidney international. 2010 Jan;77(1):37-43. PMID: 19865075.
7. Rundback JH, Sacks D, Kent KC, et al. Guidelines for the reporting of renal artery revascularization in clinical trials. American Heart Association. Circulation. 2002 Sep 17;106(12):1572-85. PMID: 12234967.
8. Balk E, Raman G. Comparative Effectiveness of Management Strategies for Renal Artery Stenosis: 2007 Update. Rockville (MD)2007.
9. Balk E, Raman G, Chung M, et al. Comparative Effectiveness of Management Strategies for Renal Artery Stenosis. Rockville (MD)2006.
10. Higgins JPT, Altman DG. Assessing Risk of Bias in Included Studies. Cochrane Handbook for Systematic Reviews of Interventions: John Wiley & Sons, Ltd; 2008. p. 187-241.
11. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [cited 2014 November 12, 2014]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
12. Berkman ND LK, Ansari M, McDonagh M, Balk E, Whitlock E, Reston J, Bass E, Butler M, Gartlehner G, Hartling L, Kane R, McPheeters M, Morgan L, Morton SC, Viswanathan M, Sista P, Chang S. . Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Comparative Effectiveness Reviews (Prepared by the RTI-UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I). 2013: Available from: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Last accessed
13. Arthurs Z, Starnes B, Cuadrado D, et al. Renal artery stenting slows the rate of renal function decline. Journal of vascular surgery. 2007 Apr;45(4):726-31; discussion 31-2. PMID: 17398382.
14. Balzer KM, Pfeiffer T, Rossbach S, et al. Prospective randomized trial of operative vs interventional treatment for renal artery ostial occlusive disease (RAOOD). Journal of vascular surgery. 2009 Mar;49(3):667-74; discussion 74-5. PMID: 19135837.

15. Bax L, Woittiez AJ, Kouwenberg HJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. Annals of internal medicine. 2009 Jun 16;150(12):840-8, W150-1. PMID: 19414832.
16. Cianci R, Martina P, Borghesi F, et al. Revascularization versus medical therapy for renal artery stenosis: antihypertensive drugs and renal outcome. Angiology. 2011 Jan;62(1):92-9. PMID: 20547539.
17. Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. The New England journal of medicine. 2014 Jan 2;370(1):13-22. PMID: 24245566.
18. Crutchley TA, Pearce JD, Craven TE, et al. Clinical utility of the resistive index in atherosclerotic renovascular disease. Journal of vascular surgery. 2009 Jan;49(1):148-55, 55 e1-3; discussion 55. PMID: 18951751.
19. de Donato G, Setacci C, Chisci E, et al. Renovascular hypertension. 8 years experience of a vascular surgery centre. The Journal of cardiovascular surgery. 2007 Aug;48(4):403-9. PMID: 17653002.
20. Dichtel LE, Gurevich D, Rifkin B, et al. Renal artery revascularization in patients with atherosclerotic renal artery stenosis and impaired renal function: conservative management versus renal artery stenting. Clinical nephrology. 2010 Aug;74(2):113-22. PMID: 20630131.
21. Hanzel G, Balon H, Wong O, et al. Prospective evaluation of aggressive medical therapy for atherosclerotic renal artery stenosis, with renal artery stenting reserved for previously injured heart, brain, or kidney. The American journal of cardiology. 2005 Nov 1;96(9):1322-7. PMID: 16253607.
22. Kalra PA, Chrysochou C, Green D, et al. The benefit of renal artery stenting in patients with atheromatous renovascular disease and advanced chronic kidney disease. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2010 Jan 1;75(1):1-10. PMID: 19937777.
23. Kane GC, Xu N, Mistrik E, et al. Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2010 Mar;25(3):813-20. PMID: 19666661.
24. Marcantoni C, Zanoli L, Rastelli S, et al. Effect of renal artery stenting on left ventricular mass: a randomized clinical trial. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2012 Jul;60(1):39-46. PMID: 22495466.
25. Ritchie J, Green D, Chrysochou C, et al. High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2014 Feb;63(2):186-97. PMID: 24074824.
26. Sofroniadou S, Kassimatis T, Srirajaskanthan R, et al. Long-term safety and efficacy of renin-angiotensin blockade in atherosclerotic renal artery stenosis. International urology and nephrology. 2012 Oct;44(5):1451-9. PMID: 22127407.
27. Uzzo RG, Novick AC, Goormastic M, et al. Medical versus surgical management of atherosclerotic renal artery stenosis. Transplantation proceedings. 2002 Mar;34(2):723-5. PMID: 12009679.
28. Wheatley K, Ives N, Gray R, et al. Revascularization versus medical therapy for renal-artery stenosis. The New England journal of medicine. 2009 Nov 12;361(20):1953-62. PMID: 19907042.

29. Ziakka S, Ursu M, Poulikakos D, et al. Predictive factors and therapeutic approach of renovascular disease: four years' follow-up. Renal failure. 2008;30(10):965-70. PMID: 19016147.
30. Patel VI, Conrad MF, Kwolek CJ, et al. Renal artery revascularization: outcomes stratified by indication for intervention. Journal of vascular surgery. 2009 Jun;49(6):1480-9. PMID: 19497511.
31. Murphy TP, Cooper CJ, Cutlip DE, et al. Roll-in experience from the Cardiovascular Outcomes with Renal Atherosclerotic Lesions (CORAL) study. Journal of vascular and interventional radiology : JVIR. 2014 Apr;25(4):511-20. PMID: 24325931.
32. Bruno RM, Daghini E, Versari D, et al. Predictive role of renal resistive index for clinical outcome after revascularization in hypertensive patients with atherosclerotic renal artery stenosis: a monocentric observational study. Cardiovascular ultrasound. 2014;12:9. PMID: 24555729.
33. Iannone LA, Underwood PL, Nath A, et al. Effect of primary balloon expandable renal artery stents on long-term patency, renal function, and blood pressure in hypertensive and renal insufficient patients with renal artery stenosis. Catheterization and cardiovascular diagnosis. 1996 Mar;37(3):243-50. PMID: 8974797.
34. Blum U, Krumme B, Flugel P, et al. Treatment of ostial renal-artery stenoses with vascular endoprostheses after unsuccessful balloon angioplasty. The New England journal of medicine. 1997 Feb 13;336(7):459-65. PMID: 9017938.
35. Harden PN, MacLeod MJ, Rodger RS, et al. Effect of renal-artery stenting on progression of renovascular renal failure. Lancet. 1997 Apr 19;349(9059):1133-6. PMID: 9113012.
36. White CJ, Ramee SR, Collins TJ, et al. Renal artery stent placement: utility in lesions difficult to treat with balloon angioplasty. Journal of the American College of Cardiology. 1997 Nov 15;30(6):1445-50. PMID: 9362400.
37. Gross CM, Kramer J, Waigand J, et al. Ostial renal artery stent placement for atherosclerotic renal artery stenosis in patients with coronary artery disease. Catheterization and cardiovascular diagnosis. 1998 Sep;45(1):1-8. PMID: 9736342.
38. van de Ven PJ, Kaatee R, Beutler JJ, et al. Arterial stenting and balloon angioplasty in ostial atherosclerotic renovascular disease: a randomised trial. Lancet. 1999 Jan 23;353(9149):282-6. PMID: 9929021.
39. Rocha-Singh KJ, Mishkel GJ, Katholi RE, et al. Clinical predictors of improved long-term blood pressure control after successful stenting of hypertensive patients with obstructive renal artery atherosclerosis. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 1999 Jun;47(2):167-72. PMID: 10376497.
40. Dangas G, Laird JR, Jr., Mehran R, et al. Intravascular ultrasound-guided renal artery stenting. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2001 Jun;8(3):238-47. PMID: 11491257.
41. Dorros G, Jaff M, Mathiak L, et al. Multicenter Palmaz stent renal artery stenosis revascularization registry report: four-year follow-up of 1,058 successful patients. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2002 Feb;55(2):182-8. PMID: 11835644.
42. Gill-Leertouwer TC, Gussenhoven EJ, Deinum J, et al. Shrinkage of the distal renal artery 1 year after stent placement as evidenced with serial intravascular ultrasound. The British journal of radiology. 2002 Nov;75(899):879-83. PMID: 12466252.

43. Ramos F, Kotliar C, Alvarez D, et al. Renal function and outcome of PTRA and stenting for atherosclerotic renal artery stenosis. Kidney international. 2003 Jan;63(1):276-82. PMID: 12472793.
44. Gill KS, Fowler RC. Atherosclerotic renal arterial stenosis: clinical outcomes of stent placement for hypertension and renal failure. Radiology. 2003 Mar;226(3):821-6. PMID: 12601202.
45. Gray BH, Olin JW, Childs MB, et al. Clinical benefit of renal artery angioplasty with stenting for the control of recurrent and refractory congestive heart failure. Vasc Med. 2002;7(4):275-9. PMID: 12710843.
46. Henry M, Henry I, Klonaris C, et al. Renal angioplasty and stenting under protection: the way for the future? Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2003 Nov;60(3):299-312. PMID: 14571477.
47. Kennedy DJ, Colyer WR, Brewster PS, et al. Renal insufficiency as a predictor of adverse events and mortality after renal artery stent placement. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2003 Nov;42(5):926-35. PMID: 14582036.
48. Zeller T, Frank U, Muller C, et al. Stent-supported angioplasty of severe atherosclerotic renal artery stenosis preserves renal function and improves blood pressure control: long-term results from a prospective registry of 456 lesions. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2004 Apr;11(2):95-106. PMID: 15056029.
49. Rocha-Singh K, Jaff MR, Rosenfield K. Evaluation of the safety and effectiveness of renal artery stenting after unsuccessful balloon angioplasty: the ASPIRE-2 study. Journal of the American College of Cardiology. 2005 Sep 6;46(5):776-83. PMID: 16139124.
50. Sapoval M, Zahringer M, Pattynama P, et al. Low-profile stent system for treatment of atherosclerotic renal artery stenosis: the GREAT trial. Journal of vascular and interventional radiology : JVIR. 2005 Sep;16(9):1195-202. PMID: 16151060.
51. Zeller T, Rastan A, Kliem M, et al. Impact of carbon coating on the restenosis rate after stenting of atherosclerotic renal artery stenosis. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2005 Oct;12(5):605-11. PMID: 16212462.
52. Rivolta R, Bazzi C, Stradiotti P, et al. Stenting of renal artery stenosis: is it beneficial in chronic renal failure? Journal of nephrology. 2005 Nov-Dec;18(6):749-54. PMID: 16358234.
53. Tsao CR, Lee WL, Liu TJ, et al. Delicate percutaneous renal artery stenting minimizes postoperative renal injury and protects kidney in patients with severe atherosclerotic renal artery stenosis and impaired renal function. International heart journal. 2005 Nov;46(6):1061-72. PMID: 16394602.
54. Holden A, Hill A, Jaff MR, et al. Renal artery stent revascularization with embolic protection in patients with ischemic nephropathy. Kidney international. 2006 Sep;70(5):948-55. PMID: 16837918.
55. Girndt M, Kaul H, Maute C, et al. Enhanced flow velocity after stenting of renal arteries is associated with decreased renal function. Nephron Clinical practice. 2007;105(2):c84-9. PMID: 17164562.
56. Ruchin PE, Baron DW, Wilson SH, et al. Long-term follow-up of renal artery stenting in an Australian population. Heart, lung & circulation. 2007 Apr;16(2):79-84. PMID: 17317314.

57. Goncalves JA, Amorim JE, Soares Neto MM, et al. Clinical efficacy of percutaneous renal revascularization with stent placement in atherosclerotic renovascular disease. Arquivos brasileiros de cardiologia. 2007 Jan;88(1):85-90. PMID: 17364124.
58. Baril DT, Lookstein RA, Jacobs TS, et al. Durability of renal artery stents in patients with transrenal abdominal aortic endografts. Journal of vascular surgery. 2007 May;45(5):915-20; discussion 20-1. PMID: 17391902.
59. Zahringer M, Sapoval M, Pattynama PM, et al. Sirolimus-eluting versus bare-metal low-profile stent for renal artery treatment (GREAT Trial): angiographic follow-up after 6 months and clinical outcome up to 2 years. Journal of endovascular therapy : an official journal of the International Society of Endovascular Specialists. 2007 Aug;14(4):460-8. PMID: 17696619.
60. Cooper CJ, Haller ST, Colyer W, et al. Embolic protection and platelet inhibition during renal artery stenting. Circulation. 2008 May 27;117(21):2752-60. PMID: 18490527.
61. Lekston A, Chudek J, Gasior M, et al. Comparison of early and long-term impact of percutaneous transluminal renal artery angioplasty alone or with brachytherapy on renal function in patients with reno-vascular hypertension. Kardiologia polska. 2008 Oct;66(10):1061-6; discussion 7-8. PMID: 19006027.
62. Rocha-Singh K, Jaff MR, Lynne Kelley E. Renal artery stenting with noninvasive duplex ultrasound follow-up: 3-year results from the RENAISSANCE renal stent trial. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2008 Nov 15;72(6):853-62. PMID: 19006254.
63. Rastan A, Krankenberg H, Muller-Hulsbeck S, et al. Improved renal function and blood pressure control following renal artery angioplasty: the renal artery angioplasty in patients with renal insufficiency and hypertension using a dedicated renal stent device study (PRECISION). EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2008 Aug;4(2):208-13. PMID: 19110785.
64. Leesar MA, Varma J, Shapira A, et al. Prediction of hypertension improvement after stenting of renal artery stenosis: comparative accuracy of translesional pressure gradients, intravascular ultrasound, and angiography. Journal of the American College of Cardiology. 2009 Jun 23;53(25):2363-71. PMID: 19539148.
65. Jokhi PP, Ramanathan K, Walsh S, et al. Experience of stenting for atherosclerotic renal artery stenosis in a cardiac catheterization laboratory: technical considerations and complications. The Canadian journal of cardiology. 2009 Aug;25(8):e273-8. PMID: 19668788.
66. Sapoval M, Tamari I, Goffette P, et al. One year clinical outcomes of renal artery stenting: the results of ODORI Registry. Cardiovascular and interventional radiology. 2010 Jun;33(3):475-83. PMID: 19908091.
67. Beck AW, Nolan BW, De Martino R, et al. Predicting blood pressure response after renal artery stenting. Journal of vascular surgery. 2010 Feb;51(2):380-5; discussion 5. PMID: 19939607.
68. Trani C, Tommasino A, Giammarinaro M, et al. Renal artery stenting in patients with chronic ischemic heart disease. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2010 Jul 1;76(1):26-34. PMID: 20578190.
69. Kobo O, Hammoud M, Makhoul N, et al. Screening, diagnosis, and treatment of renal artery stenosis by percutaneous transluminal renal angioplasty with stenting. The Israel Medical Association journal : IMAJ. 2010 Mar;12(3):140-3. PMID: 20684176.

70. Staub D, Zeller T, Trenk D, et al. Use of B-type natriuretic peptide to predict blood pressure improvement after percutaneous revascularisation for renal artery stenosis. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2010 Nov;40(5):599-607. PMID: 20739200.
71. Kawarada O, Yokoi Y, Morioka N, et al. Cardiac benefits of renal artery stenting. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology. 2010 Sep;6(4):485-91. PMID: 20884436.
72. Rzeznik D, Przewlocki T, Kablak-Ziembicka A, et al. Effect of renal artery revascularization on left ventricular hypertrophy, diastolic function, blood pressure, and the one-year outcome. Journal of vascular surgery. 2011 Mar;53(3):692-7. PMID: 21129903.
73. Rocha-Singh KJ, Novack V, Pencina M, et al. Objective performance goals of safety and blood pressure efficacy for clinical trials of renal artery bare metal stents in hypertensive patients with atherosclerotic renal artery stenosis. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2011 Nov 1;78(5):779-89. PMID: 21648052.
74. Valluri A, Severn A, Chakraverty S. Do patients undergoing renal revascularization outside of the ASTRAL trial show any benefit? Results of a single-centre observational study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2012 Feb;27(2):734-8. PMID: 21765186.
75. Mannarino A, Spatoliatore G, Caselli GM, et al. Different outcomes of atherosclerotic renal artery stenosis managed with stenting: results from a cohort study. Renal failure. 2012;34(2):142-8. PMID: 22260219.
76. Trani C, Porto I, Tommasino A, et al. Baseline inflammatory status and long-term changes in renal function after percutaneous renal artery stenting: a prospective study. International journal of cardiology. 2013 Aug 10;167(3):1006-11. PMID: 22503569.
77. Jaff MR, Bates M, Sullivan T, et al. Significant reduction in systolic blood pressure following renal artery stenting in patients with uncontrolled hypertension: results from the HERCULES trial. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2012 Sep 1;80(3):343-50. PMID: 22511402.
78. Bersin RM, Ansel G, Rizzo A, et al. Nine-month results of the REFORM study: a prospective, single-arm, multicenter clinical study of the safety and effectiveness of the Formula balloon-expandable stent for treatment of renal artery stenosis. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2013 Aug 1;82(2):266-73. PMID: 22581488.
79. Christie JW, Conlee TD, Craven TE, et al. Early duplex predicts restenosis after renal artery angioplasty and stenting. Journal of vascular surgery. 2012 Nov;56(5):1373-80; discussion 80. PMID: 23083664.
80. Cianci R, Martina P, Gigante A, et al. Predictor factors for renal outcome in renal artery stenosis. European review for medical and pharmacological sciences. 2013 Feb;17(4):507-12. PMID: 23467950.
81. Chrysant GS, Bates MC, Sullivan TM, et al. Proper patient selection yields significant and sustained reduction in systolic blood pressure following renal artery stenting in patients with uncontrolled hypertension: long-term results from the HERCULES trial. J Clin Hypertens (Greenwich). 2014 Jul;16(7):497-503. PMID: 24909590.

82. Losito A, Errico R, Santirosi P, et al. Long-term follow-up of atherosclerotic renovascular disease. Beneficial effect of ACE inhibition. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2005 Aug;20(8):1604-9. PMID: 15870215.
83. Safak E, Wilke C, Derer W, et al. Long-term follow-up of patients with atherosclerotic renal artery disease. Journal of the American Society of Hypertension : JASH. 2013 Jan-Feb;7(1):24-31. PMID: 23321402.
84. Silva VS, Martin LC, Franco RJ, et al. Pleiotropic effects of statins may improve outcomes in atherosclerotic renovascular disease. American journal of hypertension. 2008 Oct;21(10):1163-8. PMID: 18670414.
85. Webster J, Marshall F, Abdalla M, et al. Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. Scottish and Newcastle Renal Artery Stenosis Collaborative Group. Journal of human hypertension. 1998 May;12(5):329-35. PMID: 9655655.
86. Hackam DG, Duong-Hua ML, Mamdani M, et al. Angiotensin inhibition in renovascular disease: a population-based cohort study. American heart journal. 2008 Sep;156(3):549-55. PMID: 18760140.
87. Hackam DG, Wu F, Li P, et al. Statins and renovascular disease in the elderly: a population-based cohort study. European heart journal. 2011 Mar;32(5):598-610. PMID: 21156722.
88. Chrysochou C, Foley RN, Young JF, et al. Dispelling the myth: the use of renin-angiotensin blockade in atheromatous renovascular disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2012 Apr;27(4):1403-9. PMID: 21993376.
89. Alhadad A, Ahle M, Ivancev K, et al. Percutaneous transluminal renal angioplasty (PTRA) and surgical revascularisation in renovascular disease--a retrospective comparison of results, complications, and mortality. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2004 Feb;27(2):151-6. PMID: 14718896.
90. Cherr GS, Hansen KJ, Craven TE, et al. Surgical management of atherosclerotic renovascular disease. Journal of vascular surgery. 2002 Feb;35(2):236-45. PMID: 11854720.
91. Galaria, II, Surowiec SM, Rhodes JM, et al. Percutaneous and open renal revascularizations have equivalent long-term functional outcomes. Annals of vascular surgery. 2005 Mar;19(2):218-28. PMID: 15735947.
92. Demming T, Frey N, Langer C. Pickering syndrome: high-risk stenting of a renal artery stenosis in a multimorbid patient presenting with progressive congestive heart failure. Clinical research in cardiology : official journal of the German Cardiac Society. 2013 Aug;102(8):615-7. PMID: 23673780.
93. Ishida R, Komaki K, Nakayama M, et al. Percutaneous transluminal renal angioplasty remarkably improved severe hypertension and renal function in a patient with renal artery stenosis and postrenal kidney failure. Renal failure. 2013;35(4):551-5. PMID: 23473081.
94. Noce A, Canale MP, Durante O, et al. Refractory hypertension and rapidly progressive renal failure due to bilateral renal artery stenosis: case report. Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica / Associazione ricerche in urologia. 2012 Dec;84(4):249-52. PMID: 23427756.

95. Alonso JV, Caballero RM, Lopera EL, et al. Flash pulmonary edema and renal artery stenosis: pickering syndrome. The American journal of emergency medicine. 2013 Feb;31(2):454 e1-4. PMID: 22944546.
96. Chrysochou C, Schmitt M, Siddals K, et al. Reverse cardiac remodelling and renal functional improvement following bilateral renal artery stenting for flash pulmonary oedema. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2013 Feb;28(2):479-83. PMID: 22262735.
97. Navaravong L, Ali RG, Giugliano GR. Acute renal artery occlusion: making the case for renal artery revascularization. Cardiovascular revascularization medicine : including molecular interventions. 2011 Nov-Dec;12(6):399-402. PMID: 21855421.
98. George T, Latchumanadhas K, Abraham G, et al. Successful hybrid procedure in flash pulmonary edema. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2011 May;22(3):531-3. PMID: 21566313.
99. Li WS, Gilchrist M, Robertson S, et al. Bilateral renovascular disease with cardiorenal failure: intervene early or watch and wait? QJM : monthly journal of the Association of Physicians. 2012 Jun;105(6):567-9. PMID: 21558176.
100. Kindo M, Gerelli S, Billaud P, et al. Flash pulmonary edema in an orthotopic heart transplant recipient. Interactive cardiovascular and thoracic surgery. 2011 Feb;12(2):323-5. PMID: 21118836.
101. Islam MA, Rosenfield K, Maree AO, et al. Percutaneous revascularization of occluded renal arteries in the setting of acute renal failure. Vasc Med. 2009 Nov;14(4):365-9. PMID: 19808722.
102. Kanamori H, Toma M, Fukatsu A. Improvement of renal function after opening occluded atherosclerotic renal arteries. The Journal of invasive cardiology. 2009 Sep;21(9):E171-4. PMID: 19726830.
103. Dippel EJ. Percutaneous renal intervention utilizing distal embolic protection. The Journal of invasive cardiology. 2009 Aug;21(8):423-4. PMID: 19652259.
104. Dziemianko I, Kuzniar J, Dorobisz A, et al. Critical bilateral renal arterial stenosis presenting as cardio-renal syndrome: isolated ultrafiltration preceding percutaneous transluminal revascularization. Congest Heart Fail. 2009 Mar-Apr;15(2):96-8. PMID: 19379457.
105. Campbell JE, John M, Bates MC. Surgical rescue and restoration of renal function in an anuric renal failure patient: a case report. The West Virginia medical journal. 2008 Jan-Feb;104(1):22-4. PMID: 18335782.
106. Wykrzykowska JJ, Williams M, Laham RJ. Stabilization of renal function, improvement in blood pressure control and pulmonary edema symptoms after opening a totally occluded renal artery. The Journal of invasive cardiology. 2008 Jan;20(1):E26-9. PMID: 18174627.
107. Chrysochou C, Sinha S, Chalmers N, et al. Anuric acute renal failure and pulmonary oedema: a case for urgent action. International journal of cardiology. 2009 Feb 6;132(1):e31-3. PMID: 18045711.
108. Kuznetsov E, Schifferdecker B, Jaber BL, et al. Recovery of acute renal failure following bilateral renal artery angioplasty and stenting. Clinical nephrology. 2007 Jul;68(1):32-7. PMID: 17703833.
109. Kumar SC. Bilateral renal artery stenosis presenting as flash pulmonary edema. The Journal of the Association of Physicians of India. 2006 Aug;54:651-4. PMID: 16941797.

110. George PV, Pati PK, Chandy ST, et al. Recanalization of a single functioning kidney. Indian heart journal. 2005 Nov-Dec;57(6):741-3. PMID: 16521653.
111. Komatsu SO, T. Takewa, M. Takahashi, S. Nomamoto, T. Kamata, T. Nishiuchi, K. Kobayashi, Y. Kodama, K. Nonobstructive angioscopy in patient with atherosclerotic renal artery stenosis. Journal of Cardiology Cases. 2014;9(1):18-21. PMID:
112. Williamson E, Morley R, Lucas A, et al. Propensity scores: from naive enthusiasm to intuitive understanding. Statistical methods in medical research. 2012 Jun;21(3):273-93. PMID: 21262780.
113. Rubin DB. Estimating causal effects from large data sets using propensity scores. Annals of internal medicine. 1997 Oct 15;127(8 Pt 2):757-63. PMID: 9382394.
114. Dahabreh IJ, Sheldrick RC, Paulus JK, et al. Do observational studies using propensity score methods agree with randomized trials? A systematic comparison of studies on acute coronary syndromes. European heart journal. 2012 Aug;33(15):1893-901. PMID: 22711757